A REVIEW OF THE ENVIRONMENTAL AND HEALTH ASPECTS OF TRIARYL/ALKYL PHOSPHATES

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THE CONCLUSIONS AND RECOMMENDATIONS CONTAINED HEREIN REPRESENT THE OPINION OF THE CONTRACTOR AND DO NOT NECESSARILY CONSTITUTE ENDORSEMENT BY THE DEPARTMENT OF NATIONAL HEALTH AND WELFARE.

PREFACE

In 1976, the Environmental Contaminants Act was promulgated as a result of the federal government's recognition of the need to protect human health and the environment from the adverse effects of chemicals entering the Canadian environment. Responsibility for this Act rests with the Department of National Health and Welfare and the Department of the Environment.

Information initially available on the triesters of phosphoric acid indicated that this class of substances might pose a significant danger to human health or the environment. Triaryl phosphates and related substances were therefore included in Category III of the Priority and Candidate Chemicals Schedule to the Environmental Contaminants Act. For Category III substances further detailed information (for example, on toxicity and amounts used) is required to ascertain the extent of the danger.

The present review was undertaken as part of the process of gathering information on triaryl phosphates and related substances. This study was conducted by Michael Holliday and Associates under contract to the Environmental Health Directorate of the Department of National Health and Welfare; the contract was funded by the Department of the Environment and the Department of National Health and Welfare. Staff members from these departments and from the Department of Fisheries and Oceans were involved in developing the terms of reference for the study and for reviewing the contractor's draft reports.

The report provides an overview of published information on the environmental and health aspects of triaryl and tri-(alkyl aryl) phosphates, with particular reference to the situation in Canada.

The uses of these phosphate esters are reviewed and forecasts of their potential growth are given. A compilation of the physical and chemical characteristics of the esters is presented and discussed in the light of expected environmental conditions. The behaviour of the compounds in the environment is reviewed and areas are identified where information necessary for assessment of their environmental impact is lacking.

A comprehensive review of the experimental toxicology of the esters is presented, with particular attention being given to the mechanism of delayed neurotoxicity and to structure-activity relationships. A review of the effects of intoxication of humans by the esters is presented and parallels are drawn with information obtained from animal experiments.

The report concludes with a summary of the regulatory approaches adopted in a number of countries to limit exposure to triaryl phosphates.

The report also includes recommendations for topics which need further study. These are the analysis of commercial phosphate ester products; further compound by compound toxicity testing (particularly at long-term low-dose exposures); the behaviour of the esters in terrestrial media, and hydrolysis studies focusing upon the behaviour of phosphate diesters formed from the hydrolytic degradation of the triesters.

The conclusions and recommendations in this publication are those of Michael Holliday and Associates. Publication of this document should not be taken to indicate endorsement of these recommendations by any of the aforementioned federal government departments.

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SUMMARY AND RECOMMENDATIONS

SUMMARY

The literature (of which this report is a review) dealing with topics pertinent to the environmental behaviour and health implications of triaryl and tri-(alkyl aryl) phosphates is not inconsiderable. There are, however, areas in which the data are insufficient and definitive statements concerning the environmental behaviour of these phosphate esters cannot, at the present time, be made. Nonetheless the general features are apparent and are sufficient to identify areas where further research is required.

1. Commercial Uses

Triaryl and tri-(alkyl aryl) phosphates are not manufactured in Canada, but some 1300 tonnes are imported annually from the United Kingdom and the United States. They find use in two areas: as flame retardant plasticizers and as, or in, functional fluids.

The prime reason for the use of these phosphate esters is their fire retardant properties. At high temperatures (above 350° C) the esters decompose to form condensed phosphoric acids. The thermal decomposition products inhibit ignition by encouraging char formation in the hydrocarbon substrate (i. e. the plastic or functional fluid) and by acting in the gas phase to remove the free radical carriers of the combustion reaction.

A secondary reason for the utility of the phosphate esters is their excellent lubrication characteristics. For this reason they are used as additives to hydrocarbon lubricating oils. The lubricating ability is also of importance when the esters are used as fire-retarded hydraulic fluids.

The use of triaryl and tri-(alkyl aryl) phosphates in plastics accounts for 62% of their consumption in Canada (or some 800 tonnes in 1979). The greatest use of the esters is as flame retardant plasticizers in polyvinyl chloride and this accounts for about 90% of the phosphate ester use in plastics' applications. Automobile upholstery, clear film and electrical insulation are some of the end-uses of flame-retarded polyvinyl chloride. The esters also are used in paints and coatings, adhesives and certain specialty rubbers.

Some 38% (or close to 500 tonnes annually) of triaryl and tri-(alkyl aryl) phosphates are used in functional fluids. The major portion (about 85%) of this amount is used in high-pressure fluid control systems where fire retardancy is of prime importance (e. g. , hydraulic controls in steel manufacturing plants, aircraft hydraulic systems, control fluids in gas pipeline compressors and in large electricity generating steam turbines). The remaining 15% is used as additives for lubricating oils.

The overall use of triaryl and tri-(alkyl aryl) phosphates in Canada is not expected to grow significantly in the future. The use of the esters in polyvinyl chloride, aircraft hydraulic fluids and as oil additives will probably grow as there do not appear to be satisfactory substitutes. But the other uses (particularly as industrial hydraulic fluids) are expected to shrink as alternative and possibly cheaper products continue to substitute for the phosphate esters.

2. Physical and Chemical Characteristics and Analysis

There are a variety of isomeric forms possible for most triaryl and tri-(alkyl aryl) phosphates and the commercial products are commonly mixtures of esters. These factors complicate elucidation of the environmental behaviour and toxicological characteristics of phosphate esters. In manufacturing applications, it is the bulk properties of the mixture that are important. But it is a knowledge of the molecular composition of such a mixture that provides insight into its environmental and toxicological characteristics.

Pure triaryl and tri-(alkyl aryl) phosphates are generally solids at room temperature: the commercial products, however, are (with the exception of triphenyl phosphate) viscous liquids. The phosphate esters have vapour pressures of about 10^{-3} Pa at 25° C, may be distilled at reduced pressure but thermally decompose before boiling at atmospheric pressure. Water solubilities range from less than 1 mg/L to 100 mg/L, but the esters are moderately to very soluble in most organic solvents. Measured octanol/water partition coefficients range from 10^4 to 10^6. Soil sorption coefficients (soil/water partition coefficients) have been empirically calculated to be of the order of 10^4 for a few esters.

Hydrolysis of triaryl and tri-(alkyl aryl) phosphates is more rapid in alkaline media than in neutral or acidic media, and commonly occurs via nucleophilic attack by hydroxyl ions or water molecules at the phosphorus atom to yield the corresponding diesters. Hydrolysis of diesters is much slower than that for the corresponding mono- and triesters.

Photolysis of triaryl and tri-(alkyl aryl) phosphates is unlikely to occur at wavelengths greater than 290 nm. Oxidation reactions under environmental conditions are also unlikely.

The method of choice for the analysis of triaryl and tri-(alkyl aryl) phosphates is gas chromatography using a phosphorus sensitive detector, as this technique is capable of measuring individual compounds at the parts-per-billion or even the parts-per-trillion levels. At these levels concentration techniques (such as solvent extraction and absorption techniques) are required prior to chromatographic analysis. Non-specific methods such as ultraviolet or infrared spectroscopy and wet chemical methods are also used, but commonly serve merely to indicate the presence of the compounds in environmental samples.

3. Environmental Relationships

Triaryl and tri-(alkyl aryl) phosphates enter the environment from two sources: accidental spills or leaks from hydraulic systems, and from phosphate ester flame-retarded plastics. The esters have been detected in all three environmental sectors (atmosphere, aquatic and terrestrial) and in biota (specifically fish and vegetation) in samples taken from the vicinity of ester manufacturing and using facilities. Accidental intoxication has occurred in cattle from spills from pipeline compressor stations and from contamination as a result of animal husbandry. Cases of human intoxication have been reported from a number of unintentional contamination episodes.

Bioaccumulation in fish from water bodies contaminated by the esters (at ppb levels) has been recorded. This has been quantified by laboratory experiments and the bioaccumulation factors (ranging from 200 to 2500) obtained are, in general, those that would be expected from the measured octanol/water partition coefficients.

Soil sorption coefficients indicate that soil and aquatic sediments may be environmental sinks for triaryl and tri-(alkyl aryl) phosphates. Sediment samples taken from waters contaminated with phosphate esters have shown concentrations (as high as the low parts per million) about one thousand times higher than those found in the water.

Release to the atmosphere occurs mainly in the form of aerosols generated by leaks from high pressure hydraulic systems. Direct evaporation of the esters from spills, from contaminated water bodies and from flame retarded plastics may be possible but is unlikely to be significant.

The major mechanism for the dispersion of triaryl and tri-(alkyl aryl) phosphates is transport by water. However, it has also been shown that in alkaline natural waters hydrolytic degradation of the esters is fairly rapid and times ranging from one to seven days have been measured for 50% disappearance of the compounds. These disappearance rates were significantly faster than those obtained, at the same pH, in demineralized water or in sterile natural water samples. Consequently it is likely that microbial degradation is a significant if not the primary factor in removal of the triesters from aquatic systems. However, the diesters formed in such hydrolytic degradation are likely to be more persistent. They are also significantly more soluble than the corresponding triesters. The potential environmental impact of phosphate diesters has not been studied to our knowledge.

The fate of triaryl phosphates and tri-(alkyl aryl) phosphates in soil has not been definitively characterized. Microbial degradation is a probable removal mechanism and, depending on soil moisture content and pH, hydrolysis might also occur.

4. Experimental Toxicology

Studies of acute intoxication by triaryl and tri-(alkyl aryl) phosphates on species of environmental significance have been carried out on fish and cattle. In fish, absorption of the esters occurs primarily by way of gill surfaces, but oral dosing has also been shown to produce toxic effects. Gastrointestinal absorption has also been experimentally demonstrated in cattle. The symptoms are those of neurotoxicity.

Histopathology correlates with the neurotoxic signs, marked by progressive motor paralysis. Axonal degeneration is preceded by a myelin degeneration, and commences usually in peripheral systemic tracts and then progresses centrally in more severe cases. The onset of neurotoxic signs may be delayed, or remit, and then show a progressive involvement. Recovery is slow. Death may result in large dose contamination.

Studies of chronic effects in fish also show a progressive neurotoxicity. Limited changes in hematological and plasma-chemistry parameters accompany the contamination. Rainbow trout appear to be the most sensitive species.

A number of *in vitro* studies have been carried out, one showing that the phosphate esters interfere with the normal functions of sarcoplasmic reticulum. In others, a number of thermophilic fungi were shown to be able to metabolize triphenyl and tricresyl phosphates.

Many studies have shown that triaryl and tri-(alkyl aryl) phosphates can potentiate the action of organophosphorus pesticides, malathion for example, in target and non-target species. The potentiation is due to the mechanism of action of the phosphate triesters, which are inhibitory to esterases such as acetylcholinesterase. The phosphate triesters may inhibit aliesterases sensitive to malathion, for example, potentiating the effect of the latter in inhibition of neural cholinesterase.

Experimental studies using laboratory animals and procedures have yielded the most basic information on triaryl and tri-(alkyl aryl) phosphate effects and modes of action. Absorption by way of skin or gut is rapid in mammals, as is loss by way of urine, bile and feces. Storage occurs in a variety of body tissues, most predominantly in the liver which is the site most identified with phosphate ester metabolism.

Acute toxicity effects in studies on laboratory animals relate particularly to the antiesterase activity of triaryl and tri-(alkyl aryl) phosphates, leading to paralysis, dyspnea and death. Delayed neurotoxicity follows one to two weeks without symptoms after the poisoning event. This commences with a flaccid paralysis and ataxia of the rear limbs, progressing to the forelimbs and perhaps involving trunk musculature in severe cases. The degree of involvement is dose-dependent as well as depending on the phosphate ester.

Of the many laboratory test species studied, the chicken and cat appear to be the most sensitive and representative of human toxicities. Neuropathology shows the primary lesion to be axonal, leading to demyelination and a decrease in the conductive velocity of nerve impulses. Neurotoxicity, particularly for tri-o-cresyl phosphate, has been described as a Wallerian degeneration.

Structure-activity relationships show that the formation of a saligenin cyclic aryl phosphate metabolite from a triaryl phosphate containing at least one o-alkylphenyl ester group is positively linked to neurotoxicity. From studies of a large number of triaryl phosphates it has been concluded that delayed neurotoxic activity requires an ortho-alkyl group with at least one hydrogen atom on the alpha-carbon. Triaryl phosphates with only one aryl group containing such an o-alkyl substituent are more toxic than those with two or three such o-alkylphenyl groups.

In summary, the major expression of triaryl and tri-(alkyl aryl) phosphate poisoning is one of delayed neurotoxicity. Tremendous differences exist in the toxic effects of the various phosphate triesters, ranging from the highly neurotoxic cresyl diphenyl phosphate, which has a minimum dose effect level of 10 to 15 mg/kg in hens, to some probably non-toxic tri-(alkyl aryl) phosphates which have effect levels in excess of 5 g/kg. All species examined are susceptible to triaryl and tri-(alkyl aryl) phosphate poisoning, but to a variable degree depending on species type, age, sex, condition and route of exposure.

5. Human Toxicology

The information regarding the human toxicology of triaryl and tri-(alkyl aryl) phosphates is based on a small number of critical intoxication events. These were, for the most part, accidental or episodic in nature.

Acute intoxication by ingestion is commonly associated with nausea, vomiting, abdominal cramps, and diarrhea as early signs. At a given dose, the severity of the immediate effects appears to show a great individual variability. Further, the degree of acute effects bears little relation to the degree of delayed symptoms, marked by the development of paralysis. The delayed paralysis effect may occur one week to a month after an acute exposure, or take much longer to develop in instances of low level chronic exposures. There is some suggestion that the neurological effects are additively dose-dependent; in that, long-term low dose exposure appears to show an almost direct relationship to the cumulative dose level.

The delayed neurological effects involve long axon sensory and motor nerves. The effects are progressive and generally commence in lower extremities. Muscular cramps, soreness, numbness, and tingling sensations in the feet, calves and thighs are followed by flaccid paralysis in the toes. The paralysis, if unchecked by removal from exposure in cases of chronic contamination, gradually extends proximally to involve the legs. In instances of high dose exposure or presumably high individual sensitivity, the neuropathology may extend to the upper spinal cord and show consequent paralysis of the hands and arms. The upper central nervous systems and the autonomic nervous system are little affected. Clinical diagnosis of phosphate triester intoxication, acute or chronic, was limited to depressed cholinesterase activity, particularly of blood pseudocholinesterase.

In summary, the picture of human poisoning closely approximates the animal models, including the delayed appearance of neurological signs, long recovery times, and the lack of positive correlation between overt effects and blood cholinesterase changes. Nonetheless, the measure of cholinesterase activity can be used as an early diagnosis even in chronic exposure. Although almost all the information on human toxicity effects specifies or implicates tri-o-cresyl phosphate as the toxicologically active compound, it is reasonable to assume that other phosphate triesters will have effects in humans similar to those shown in experimental toxicological studies.

6. Regulatory Approaches

The regulatory approaches taken by 17 countries for which it was possible to obtain some information cover a whole range of options: workplace exposure levels, compensatable industrial diseases, labelling requirements, allowable concentrations in drinking water, disposal guidelines, and allowable additives in food packaging. But no country was determined to have a comprehensive set of regulations dealing with triaryl and tri-(alkyl aryl) phosphates.

The area of most common agreement was in regulations or guidelines for occupational exposure to triaryl phosphates. Two compounds, tri-o-cresyl phosphate and triphenyl phosphate, have received the widest attention. The values chosen by the 12 countries having occupational exposure limits correspond with the American Conference of Governmental and Industrial Hygienists' Threshold Limit Values of 0.1 mg/m^3 and 3 mg/m^3 for tri-o-cresyl and triphenyl phosphates, respectively.

RECOMMENDATIONS

1. Analysis of Commercial Products

There is little information concerning the actual composition of commercial triaryl and tri-(alkyl aryl) phosphate products, and the existing information is, at times, ambiguous and unclear. It would therefore be appropriate to analyze commercially available products in order to identify the individual phosphate esters that could find their way into the Canadian environment. The analytical method used must be capable of identifying and quantifying the components of a commercial mixture in an unchanged form. (Analytical methods that require the breakdown of the phosphate ester into its constituent phenols and/or alcohols will not provide the necessary information on which to base a toxicological assessment.)

2. Toxicological Testing

Complementary to the analytical approach recommended above there is a need to establish unambiguous toxicity testing procedures, both to define a compound by compound toxicity scale (unaffected by the presence of trace impurities which may have considerably higher toxicity than the test compound) and to better define differences in species' response. Studies, particularly in species of economic importance (e. g. fish, cattle), into the effects of long-term low-level exposure to the phosphate esters would also be of value.

3. Studies on Environmental Transport and Degradation

Calculated soil sorption coefficients suggest that soil may be an environmental sink for triaryl and tri-(alkyl aryl) phosphates. Most phosphate esters are used as flame-retardant plasticizers in polyvinyl chloride, and the majority of plastic material is eventually disposed of in landfill sites. Nothing is known concerning the potential for phosphate esters to migrate from plastics into soil, and little is known concerning transport and degradation of the phosphate esters once they are adsorbed in soil. There is, therefore, need for further studies into the behaviour of triaryl and tri-(alkyl aryl) phosphates in the terrestrial environment.

There is also a need for studies which focus attention on the phosphate diester products formed when triaryl and tri-(alkyl aryl) phosphates are hydrolysed. Laboratory kinetic studies indicate that the diesters may be much more persistent in aquatic media than the triesters. Should such a persistence be demonstrated (by both laboratory kinetic studies and by measurement of diesters in environmental samples), toxicity studies of the phosphate diesters will need to be carried out in order to assess their environmental impact.

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The work presented in this report was aided by valuable co-operation from federal and provincial departments, and from representatives of Canadian industry. The bulk of the literature search necessary to this project was capably carried out by our researcher, Ramiro Trucco. We are also indebted to the review committee for helpful and constructive criticism of the draft report. Many of its suggestions have been incorporated into the final report.

1. INTRODUCTION

1.1 BACKGROUND

Organophosphate esters, particularly triaryl and tri-(alkyl aryl) phosphates (referred to collectively as triaryl/alkyl phosphates, or TAP/AAPs, throughout this report), are widely used in consumer and industrial products where fire retardancy is a desirable or mandatory requirement. The esters are not manufactured in Canada but some 1300 tonnes are imported annually. The two major uses are as plasticizers in polyvinyl chloride (56%) and in functional fluids (38%).

Although the esters have been known for over a century (triphenyl phosphate was first prepared in 1854[1]) their first commercial use, as plasticizers for cellulosic materials, occurred in the second decade of this century.[2] Nowadays they are used as fire retardant plasticizers in automobile and household goods and as functional fluids in foundries and pipeline compressor stations, hydraulic control fluids in large electricity generating turbines and hydraulic fluids in aircraft. Because of their lubricating properties they are also used as additives in lubricating oils.

The principal cause for concern from an environment/health standpoint is the ability of certain TAP/AAPs (particularly tri-o-cresyl phosphate) to cause delayed neurotoxicity in animals. This toxic effect manifests itself as progressive paralysis which in severe cases leads to death. Numerous instances of accidental poisoning have been reported, over the last 50 years, in humans and in farm animals. Similar effects have been experimentally demonstrated in fish.

Triaryl/alkyl phosphates may enter the environment through accidental spills and leaks from hydraulic systems, disposal of waste oil and functional fluids, and leaching of TAP/AAP plasticizers from plastic goods in waste disposal sites. Traces of TAP/AAPs have been found in samples taken from atmospheric, aquatic and terrestrial sources. The substances tend to concentrate in aquatic sediments and possibly in soil. Bioaccumulation has been observed in fish. Hydrolytic and microbial degradation are likely to be the major processes for TAP/AAP removal.

In 1979 Canada designated triaryl phosphates and related substances as Category III substances for review under the Environmental Contaminants Act.[3] Category III substances are defined as those "which may pose a significant danger to human health or the environment and about which further detailed information (for example, toxicology and amounts used) is required."

This report is a component of the information gathering exercise.

1.2 SCOPE

Eleven TAP/AAPs were identified by the Department of the Environment and the Department of National Health and Welfare for consideration in this study:

triphenyl phosphate	TPP
tricresyl phosphates (tri-o-cresyl phosphate)	TCP TOCP

trixylyl phosphates	TXP
cresyl diphenyl phosphate	CDP
isopropylphenyl diphenyl phosphate (mixed isopropylphenyl/phenyl phosphates)	IPDP
t-butylphenyl diphenyl phosphate (mixed butylphenyl/phenyl phosphates)	BPDP
tri-isopropylphenyl phosphate	TIPP
nonylphenyl diphenyl phosphate	NPDP
dibutyl phenyl phosphate	DBPP
2-ethylhexyl diphenyl phosphate	EHDP
isodecyl diphenyl phosphate	IDDP

This report is a review of published information on these compounds. In conducting this review, areas where data pertinent to assessing the compounds' environmental impact are lacking are identified. Recommendations are also made as to further studies that might be carried out in the light of such lack of information.

1.3 FORMAT

The extent to which TAP/AAPs are used in Canada is the starting point to any discussion of the environmental and health effects of the compounds. Accordingly, the report starts with a chapter describing the commercial aspects of TAP/AAPs: their uses and their consumption.

This is followed by a chapter dealing with the physical and chemical characteristics of the esters, and the analytical techniques used in their measurement. Attention is drawn to the role of structure on TAP/AAP characteristics, and to the difficulty of identifying individual TAP/AAP compounds.

A review is presented of the transport and degradative mechanisms of TAP/AAPs in the environment. Those pathways and mechanisms confirmed by experimental evidence are identified. Because the picture is incomplete, published information concerning speculative aspects of transport and degradation are also presented.

Two chapters are devoted to toxicological aspects. The first deals with environmental toxicology, presenting data on both biota of environmental importance and on experiments with laboratory species. Highlighted are the effects of structure on toxicity and the toxicity variations between different species. Information dealing with the mechanism(s) of neurotoxicity is critically reviewed. The second, on human toxicology, presents information obtained from mainly episodic cases of accidental intoxication. Parallels are drawn between results of animal experiments and observed clinical effects in man.

The final chapter presents information on regulations and guidelines on TAP/AAPs in a number of countries. While for any one country the regulatory approach is not comprehensive, many different types of regulations are used in the countries for which information was obtained. These approaches range from the very general (designation of some TAP/AAPs as toxic) to the more specific (permissible workplace exposure limits), designation of TAP poisoning as a compensatable disease, and identifying certain TAPs as permissible additives in food packaging materials.

2. COMMERCIAL ASPECTS OF TRIARYL/ALKYL PHOSPHATES IN CANADA

2.1 INTRODUCTION

Triaryl/alkyl phosphates are not manufactured in Canada. But it is estimated, on the basis of published information and conversations with industry representatives, that some 1300 tonnes annually are imported (see Section 2. 3).

Table 2-1 lists the primary suppliers, the trade names of the products and the principal component of each product. These commercial products are often mixtures of a number of phosphate triesters (see Chapter 3).

This chapter deals with the uses to which TAP/AAPs are put in Canada, their consumption and estimates of their future use.

2.2 USES

The two major uses of TAP/AAPs are as plasticizers and as functional fluids. Functional fluids is a term used to describe products (e. g. , hydraulic fluids, lubricating oils) used to fulfil a mechanical function, rather than products incorporated into a plastic matrix.

The single largest use is as a flame retardant plasticizer in polyvinyl chloride (PVC); other uses as plasticizers are very limited. Functional fluids containing TAP/AAPs can be divided into five use

TABLE 2-1 Commercial Triaryl/alkyl Phosphates Sold in Canada in 1979

Company	Trade Name	Major Constituents*	Abbreviation
Ciba-Geigy	Reofos 50 Reofos 65 Reofos 95 Reofos 110 Reolube HYD70 Reolube HYD110 Reolube HYD350	Tri-isopropylphenyl phosphate Di-isopropyl-phenyl phenyl phosphate Isopropylphenyl diphenyl phosphate	TIPP IPDP
Stauffer	Fyrquel GT Phosflex 51B Phosflex 41B**	t-Butylphenyl diphenyl phosphate Isopropylphenyl diphenyl phosphate	BPDP IPDP
Monsanto	Santicizer 141	2-Ethylhexyl diphenyl phosphate	EHDP
	Santicizer 148	Isodecyl diphenyl phosphate	IDDP
	Skydrol LD4**	Tributyl phosphate Dibutyl phenyl phosphate	DBPP
	Skydrol 500B	Tributyl phosphate Dibutyl phenyl phosphate	DBPP
Chevron	Chevron - 4	Tributyl phosphate Trialkylphenyl phosphate	
Erco	Pliabrac 521 Pliabrac 524	Unspecified synthetic triaryl phosphates	
	Tricresyl phosphate - Regular	Tricresyl phosphate (natural)	TCP
	Tricresylphosphate - X grade	Trixylyl phosphate (natural)	TXP
	Cresyl diphenyl phosphate	Cresyl diphenyl phosphate (natural)	CDP
F.M.C. (through Canada Colour and Chemical Ltd.)	Kronitex TGP	Tricresyl phosphate (natural)	TCP

* The chemical name given is that of the principal compound(s).

** These products have only recently been introduced into the Canadian marketplace.

NOTE: This table includes only those compounds currently being sold in Canada. There are additional triaryl and trialkyl/aryl phosphates available from the above manufacturers but suppliers report no customers for them at the present time.

The description "natural" and "synthetic" are used by the manufacturers to differentiate those TAP/AAPs which are produced from cresylic acid (a mixture of phenol, cresols and xylols) from those made from definite mixtures of phenols (and alcohols).

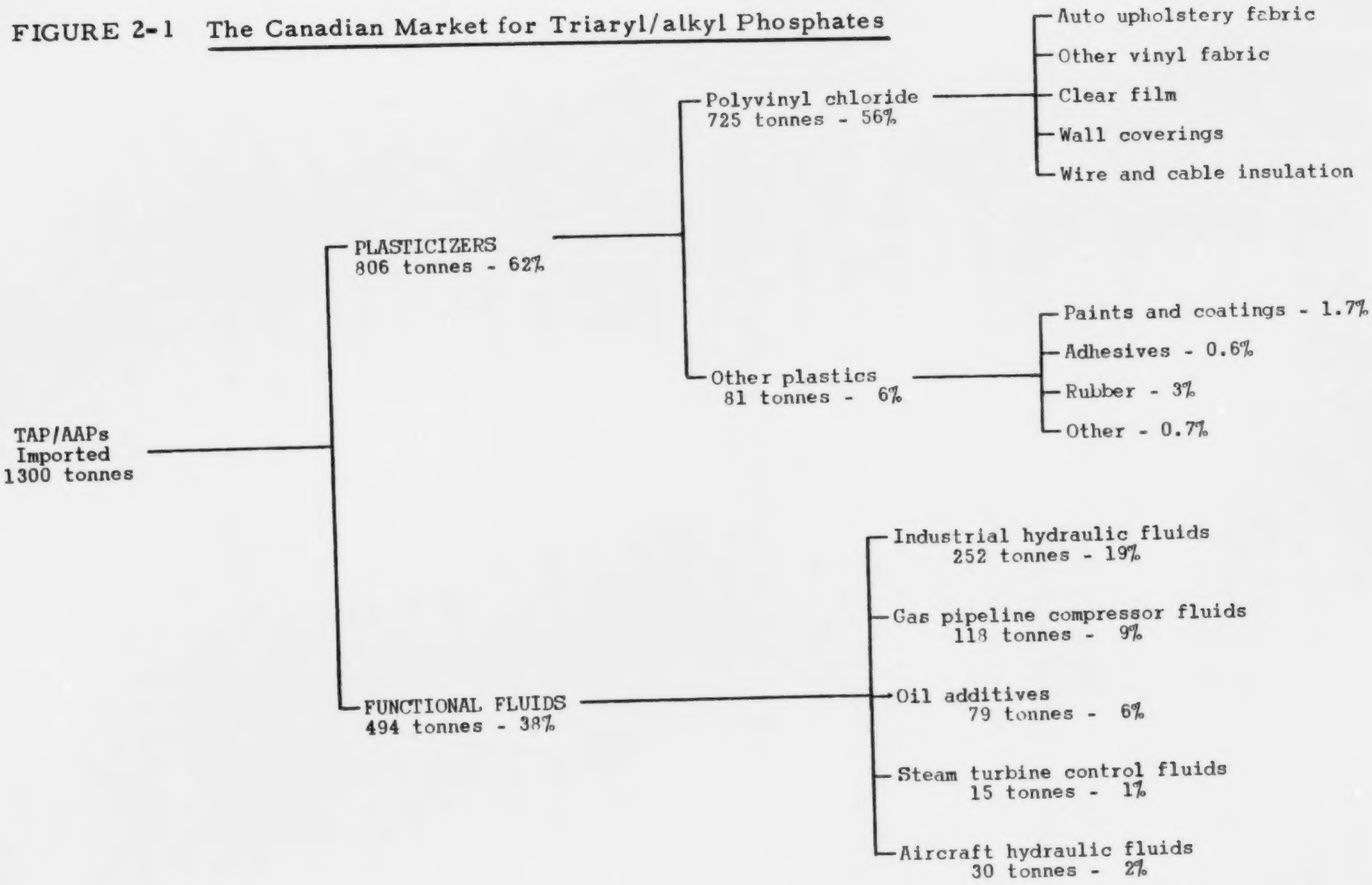
categories: industrial hydraulic fluids, gas transmission compressor fluids, oil additives, steam turbine control fluids, and aircraft hydraulic fluids. There are other minor uses of TAP/AAPs. but such uses account for less than 10% of the total market and are discussed under the general category of plastics.

Figure 2-1 outlines the Canadian marketplace for TAP/AAPs. The quantities given in this figure are estimates for 1979 based on information provided by the suppliers. The percentages of the total consumption of TAP/AAPs used in each major area are summarized in Table 2-2. It can be seen that the major demand for these compounds is for the manufacture of PVC (56%). The second most important area of demand is for industrial hydraulic fluids (19%). No other single use represents more than 10% of total consumption; the next largest use being in natural gas pipeline pumping stations which accounts for 9% of total consumption.

2.2.1 Plastics

Triaryl and tri-(alkyl aryl) phosphates are excellent flame retardant plasticizers for PVC. A study of the 1976 use of flame retardants in Ontario did not identify TAP/AAPs as being used in any plastics other than PVC.[4] The report did identify other uses than as flame retarding plasticizers. These were in the formulation of adhesives, inks, and coatings. Conversations with industry indicate that these other uses are declining. By projecting 1976 data and qualifying it by what industry has indicated to be the current situation, it may be estimated that at least 90% (725 tonnes) of TAP/AAPs used as flame retardants in plastics (i. e., non-functional fluid uses) are

FIGURE 2-1 The Canadian Market for Triaryl/alkyl Phosphates



NOTE: The quantities refer to 1979 consumption

The percentage of the total TAP/AAP market held by each use category is also shown

TABLE 2-2 Uses of Triaryl/alkyl Phosphates as Percentages of Total Canadian Market in 1979

Plasticizers	62%
PVC	56%
Paints and coatings	2%
Adhesives	1%
Rubber	3%
Other	1%
Functional Fluids	38%
Industrial hydraulics	19%
Gas transmission lines	9%
Oil additives	6%
Aircraft hydraulics	2%
Steam turbines	1%

employed in PVC.

In the United States the phosphate esters are the major flame retardant used in PVC.[5,6] In 1976 the esters accounted for 50% of the flame retardants used in this plastic and this amount corresponded to 83% of all TAP/AAP plasticizer use.[5] The Canadian marketplace is believed by industry to be very similar to that in the United States.

Other flame retardants, such as antimony trioxide, are not plasticizers and have to be used in conjunction with a plasticizer. Polyvinyl chloride resin itself is inherently flame retardant so for rigid PVC, which does not contain a plasticizer, no flame retardants need to be added. (Rigid PVC accounts for 45% of the PVC consumed in Canada.[7]) The addition of a plasticizer reduces the overall chlorine content, thereby increasing the flammability and, should a phthalate plasticizer be used, it further increases the flammability by providing a higher percentage of flammable material in the system.[6] About 20% of all PVC produced is treated with flame retardants.

There are four major uses of flame retarded PVC: automobile upholstery fabric, wire and cable coatings, vinyl film, and vinyl wall coverings. While phosphate esters are the preferred flame retardants because they also act as plasticizers, the rising price of these esters relative to other flame retardants has caused users to seriously consider using cheaper alternatives. The most common alternative is antimony trioxide used in conjunction with phthalate plasticizers. In certain applications, however, antimony trioxide cannot be used because it has an undesirable pigmenting effect on the final product which prevents good colour matching. Where clear film is being made or where dark colours have to be matched the phosphate esters are the only appropriate flame retardants.

The three groups of phosphate triesters used as flame retardant plasticizers -- triaryl, tri-(alkyl aryl) and trialkyl phosphates -- have slightly different properties which tend to favour their uses in different applications. Triaryl phosphates are the most effective flame retardants and tri-(alkyl aryl) phosphates are the most effective plasticizers. Trialkyl phosphates are least effective as flame retardants but have exceptionally good low temperature plasticizing characteristics.[6] Unfortunately there is insufficient information available to define the Canadian use patterns of the individual compounds. With the exception of TCP, there is only one supplier of each of the compounds under consideration (see Table 2-1) so that use information for individual compounds is confidential to the supplier concerned.

Other uses of TAP/AAPs in plastics include an estimated 3% employed by the rubber industry as a flame retardant plasticizer. As with PVC manufacture, the choice of TAP/AAP in these rubber manufacturing applications depends on the combination of flame retardancy, plasticity and low temperature characteristics desired.

The paint and coatings industry probably accounts for approximately 2-3% of the use of TAP/AAP compounds consumed in Canada. The compounds are used by the paint industry as a dispersant for colour pigments. The same pigments also are used in various thermoplastics such as ABS.[8] The other use of TAP/AAPs in coatings include acrylic lacquer automobile paints and in nitrocellulose lacquers for furniture finishes.[8] Industry spokesmen indicate that the paint and coatings markets are not growth areas for TAP/AAPs.

The only remaining use of TAP/AAPs that has been identified in Canada is as an adhesive additive.[4] Where flame retardancy is required in such products as laminates, the laminating adhesive may be plasticized with a phosphate ester.[8] United States' data suggest that this could account for as much as 1% of consumption of these compounds in non-functional fluid uses.

2.2.2 Functional Fluids

Triaryl/alkyl phosphates are used in or as functional fluids because of their fire resistant characteristics. The uses of functional fluids containing these compounds will be considered under the five separate categories referred to below.

The first three categories -- industrial hydraulic fluids, gas pipeline compressor fluids and steam turbine control fluids -- represent situations where the functional fluid would be predominantly TAP/AAPs. In the case of oil additives and aircraft hydraulic fluids TAP/AAPs are not the major ingredients.

2.2.2.1 Industrial hydraulic fluids: Wherever a hydraulic system operates in conjunction with a high temperature process, a severe fire hazard can only be avoided by the use of non-flammable or fire retardant hydraulic fluids. Triaryl/alkyl phosphates are not only fire retardant but also have excellent antiwear characteristics which make them an ideal choice for hydraulic fluids in these areas.

The two major industries currently using these hydraulic fluids are the steel industry and the automotive industry (engine plants).

In the steel industry the hydraulic control systems of the blast furnace doors are generally filled with a phosphate ester fluid. Other hydraulic systems in a steel mill where, if a line leaks or fractures the hydraulic fluid could come in contact with hot metal, probably use a fire retardant hydraulic fluid.

Similarly in plants where automotive engine blocks are being cast, the hydraulic control systems for the casting operations use fire retardant hydraulic fluid. Fire retardant hydraulic fluids are probably used in the majority of metal die casting and foundry operations but this section of the marketplace is seen as being insignificant compared to the two abovementioned industries.

The escalating price of the phosphate ester hydraulic fluids has caused industry to look for cheaper fire retardant hydraulic fluids. There is some indication that cheaper water/glycol hydraulic fluids are replacing the phosphate esters in the industrial uses.[10]

It is estimated, from information provided by suppliers, that phosphate ester industrial hydraulic fluids account for about 51% of the TAP/AAP functional fluids consumed in Canada, or about 252 tonnes in 1979.

2.2.2.2 Gas pipeline compressor fluids: Given the flammable nature of natural gas, it is essential that the fire hazards at compressor stations along the gas transmission lines be reduced to a minimum. The compressors, therefore, operate using fire retardant functional fluids. As with the industrial hydraulic fluids there are indications that the cheaper water/glycol based fluids are gaining importance in this marketplace.[11] It is estimated that this use of phosphate ester functional fluids accounts for about 24% (118 tonnes) of current Canadian consumption of these compounds.

2.2.2.3 Steam turbine control fluids: The very large steam turbines used in some newer power stations, have hydraulic control systems and the control fluid usually specified by the turbine manufacturer is a triaryl phosphate. Older, smaller power stations use mechanical control systems and hydro generated power has neither the higher temperature condition nor the variable energy input which require fire retarded control systems.

The control fluid for large steam turbines is contained in reservoirs which take about 4500 L of phosphate ester fluid. These reservoirs are kept fully charged. The quantity of phosphate ester functional fluids sold for this use depends not only on the regular replacement but also on construction of new turbines. It is estimated that, for 1979, this use accounted for approximately 2% (15 tonnes) of the TAP/AAP functional fluids consumed in Canada.

2.2.2.4 Oil additives: As previously mentioned the TAP/AAPs give excellent antiwear characteristics to functional fluids. In addition to antiwear characteristics, they also have excellent extreme pressure characteristics.[9] These desirable characteristics result in a fairly widespread use of the compounds as additives to hydrocarbon based fluids. These fluids may be either lubricants or hydraulic fluids, or, in some situations, both.

The concentration of the triaryl or tri-(alkyl aryl) phosphate in these oils is usually less than 2% and frequently as low as 0.5%. According to a U.S. report, oils containing these additives may go into a wide variety of uses as: cutting oils in metal fabrication, machine oils (particularly for copper and brass), steam turbine oils, farm machinery hydraulic and transmission fluids, marine type gear oils, automotive and truck transmission fluids, some types of shock absorbers on railway freight cars, and cooling lubricants for commerical refrigeration.[8] Information from industry suggests that 6% (79 tonnes) of all the TAP/AAPs being consumed in Canada go into oil additives.

2.2.2.5 Aircraft hydraulic fluids: Commercial aircraft are required by regulation to use fire retardant hydraulic fluids. These aircraft hydraulic fluids differ from the industrial hydraulic fluids discussed in Section 2.2.2.1 in that they are based on a trialkyl phosphate, usually tributyl phosphate. This trialkyl phosphate is blended with smaller quantities of a tri-(alkyl aryl) phosphate and an additive package.[13] The tri-(alkyl aryl) phosphate commonly used is dibutyl phenyl phosphate.[8] The different aircraft hydraulic fluids available vary in their additive packages and, to a lesser extent, the relative proportions of alkyl to alkyl aryl phosphate. It is possible that the additives used in these fluids may also contain phosphate esters. Information from commercial and military users suggests consumption of tri-(alkyl aryl) phosphate for aircraft hydraulic fluids to be in the region of 2% of total TAP/AAP consumption in Canada, or some 30 tonnes in 1979.

2.3 FACTORS HAVING A BEARING ON CONSUMPTION

The information on the consumption of TAP/AAPs given here was gathered from suppliers and, to a lesser extent, major users. None of the TAP/AAPs are manufactured in Canada but are imported from the United Kingdom and the United States; about 64% of the total supply of these products comes from the United Kingdom.

The major suppliers sell directly to their major customers and indirectly, through distributors, to smaller customers in specialized markets. It is probable that TAP/AAPs are also imported into Canada as additives already blended into certain oils which are sold through distributors. It is not known how much of the TAP/AAPs will enter Canada indirectly through suppliers other than the major suppliers listed in Table 2-1.

It is estimated that, in 1979, a total of approximately 1,300 tonnes of TAP/AAPs were imported into Canada.

The only triaryl phosphate for which published import data are available is tricresyl phosphate. Imports of TCP for the years 1976 to 1979 are given in Table 2-3. It can be seen that there has been a startling drop in imports of TCP since 1977. This probably represents the combination of two effects: a shift to other TAP/AAPs, and a shift to other additive products that are cheaper than the triaryl phosphates.

The price of TAP/AAPs has increased steadily over the last few years. The price of the natural based TCP and TXP has increased faster than the prices of the synthetic TAP/AAPs. The drop in imports

TABLE 2-3 Imports of Tricresyl Phosphate[12]

	Tonnes
1976	447
1977	555
1978	384
1979	124

of TCP is, therefore, probably a reflection of the increase in its price relative to the price of alternative compounds.

A previous Canadian study of the market for TAP/AAPs estimated consumption in 1977 to be 1360 tonnes or less.[11] It is estimated on the basis of information gathered for this study that in 1979 consumption was 1300 tonnes or less. These findings confirm the opinion of industry that the marketplace is fairly static, shrinking in those areas where alternative products are available and growing slightly where no substitutes are available.

2.4 THE FUTURE MARKET

It is difficult to forecast the future usage of TAP/AAPs. A variety of factors is at work in the marketplace and their effects cannot easily be isolated. The marketplace is moving towards substitutes for these phosphates wherever possible. In the long term the only remaining uses will be in situations where no acceptable substitute is available at reasonable cost. A United States study stated: "Confusion regarding the future of these chemicals is based on the environmental and toxicological concerns regarding these chemicals, particularly TCP and CDP; the substantial increase in costs of cresol (cresylic acid) since 1974, the increasing need for fire resistant functional fluids and flame retardant plasticizers, of which triaryl phosphates are among the best; and the development of less expensive substitutes for major use categories".[8] This statement applies equally well to the Canadian marketplace. The future of these compounds for each of the major use categories is discussed below.

2.4.1 Plasticizers

The use of TAP/AAP plasticizers in PVC is already restricted to those applications where combinations of other flame retardants and plasticizers are unsatisfactory (see Section 2.2.1). This is, however, still a growth area, dependent to a large extent on the automobile industry. If the current decline in automobile production continues it could have a noticeable effect on consumption of TAP/AAPs in Canada. Industry expects the use of PVC, flame retarded with TAP/AAPs, in other products than automobiles to grow slowly.

The other non-functional fluid uses of these compounds (see Figure 2-1) are, in the opinion of industry, declining. These other uses represent only 6% of the total marketplace and so are not particularly significant.

2.4.2 Functional Fluids

The use of TAP/AAPs as functional fluids accounts for approximately 38% of current consumption. The use of these compounds in industrial hydraulic fluids and natural gas pipeline pumping stations is thought, by industry, to be declining. Water/glycol mixtures are cheaper than TAP/AAPs and are taking an increasing share in these two markets. There is no reason to expect any change in this trend. These two uses, industrial hydraulic fluids and natural gas pipeline pumping stations, currently account for 75% of the TAP/AAPs consumed as functional fluids. A decline in such a major section of the marketplace will have a significant effect on the overall consumption pattern.

The use of these compounds in oil additives is not expected to decrease. These compounds impart specific characteristics to the oil and no other compounds are thought to function as effectively.[10] This section of the marketplace may be expected to grow steadily.

In steam turbines, the use of these compounds will depend on construction of new large nuclear or large fossil fuel power stations. This is a small section, 1%, of the market, but may be expected to grow slightly unless the equipment manufacturers relax their specifications for the control fluids to be used, in which case this market could disappear completely.

Aircraft hydraulic fluids currently account for 2% of the overall consumption of TAP/AAPs in Canada. A new aircraft hydraulic fluid has apparently been recently introduced into the Canadian marketplace - Skydrol LD4 - this is thought to contain as much as 31% DBPP. A major consumer of aircraft hydraulic fluid was of the opinion that this new fluid, being lighter in weight than those previously available, may take a large part of this market.[13] If this occurs it will substantially increase the consumption of TAP/AAPs by this industry as the fluids currently used are believed to contain only 12% DBPP.

In overall terms the market for TAP/AAPs in functional fluids is not expected to grow because the major use categories -- industrial hydraulic fluids and gas transmission compressors -- are already switching to other fluids. The other use categories may be expected to grow but their growth would not be sufficient to compensate for the contraction expected in the major use categories.

2.4.3 The Future of the Total Marketplace

An increasingly large share of the TAP/AAPs consumed in Canada will probably go into PVC. This is the only major use category which is expected to grow. The other growth areas are the use of these compounds as oil additives, aircraft hydraulic fluids, and possibly steam turbine control fluids. In all other use areas other products are currently being substituted for TAP/AAPs wherever possible.

It should be noted that substituting other compounds for TAP/AAPs in functional fluid applications is usually a major task in any existing system since seals compatible with phosphate esters are rarely compatible with alternative functional fluids.[10] The indications are that this kind of system modification is being considered by some end-users.

In the long term it appears that TAP/AAPs will price themselves out of the marketplace for all but the few uses (such as specific grades of PVC, oil additives, and aircraft hydraulic fluids) where there are no currently acceptable substitutes. It is possible, however, that new compounds will be developed which may substitute for TAP/AAPs in these uses. The development of satisfactory alternative compounds has not been investigated for this report.

3. PROPERTIES, CHARACTERISTICS AND ANALYSIS

3.1 INTRODUCTION

A complicating factor in any discussion of triaryl/alkyl phosphates is the variety of their isomeric forms. In addition, commercial products are commonly mixtures of esters, the exact composition of which depends not only on the combination of phenols (and alcohols) used in their manufacture but also on the physical conditions under which they were produced.

A complete assessment of the environmental and health implications of these commercial products would ideally be based on identification of all the component TAP/AAPs of which they are comprised and on the properties (physical, chemical, toxicological) of each constituent. This information is, at best, incomplete and, in many instances, lacking. Only in the last few years have analytical methods been developed that enable direct identification of individual constitutents. Indirect methods that identify breakdown products (e. g. hydrolysis products) and non-specific methods (e. g. colorimetry) have been used for a greater length of time.

This chapter reviews published material dealing with structure and identity of the compounds, their physical and chemical characteristics and the methods used in their analysis.

The section on structure and identity highlights the various isomeric forms possible for a given ester and the various phosphates that can result from the phosphorylation of a mixture of phenols (and alcohols). It is knowledge of a mixture's molecular composition that provides an insight into its environmental and toxicological behaviour.

Physical properties of pure compounds and commercial mixtures are discussed separately. (Additional data specific to environmental distribution -- vapour pressures of commercial products, solubilities of impure single compounds and their octanol/water partition coefficients -- are presented in the following chapter in Sections 4. 5. 1. 1 and 4. 5. 2. 1.) In commercial applications, it is the bulk properties of the mixture that are important. On release to the environment it is the properties of the individual components that attain greater importance.

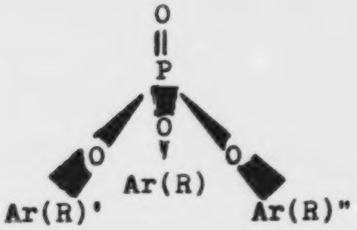
In the section dealing with chemical properties a brief description of the chemistry of ester manufacture (which is not carried out in Canada) is given because it is pertinent to the composition of the commercial product. Brief accounts of the mechanism of fire retardancy and of the plasticizing effects are provided. The reactions involved in hydrolysis of the esters are reviewed, as these reactions play an important part in ester degradation.

While attention is focused upon modern analytical methods for direct identification and quantitation of the esters, methods of a more general nature are also mentioned. The latter have been, and still are, used in general investigations of the presence of the esters in environmental samples.

3.2 STRUCTURE AND IDENTITY

3.2.1 Structure

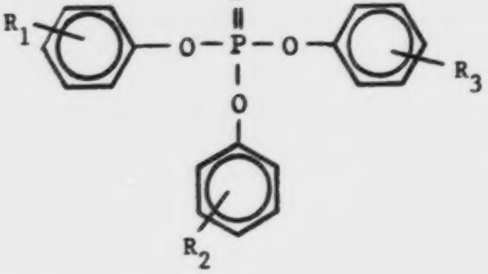
The triaryl/alkyl phosphates are essentially tetrahedral in shape:



where the aryl(alkyl) groups, Ar(R), Ar(R)' and Ar(R)", may be the same or different. The O-P-O bond angles are close to 109° suggesting that, in valence-bond theory nomenclature, the central phosphorus atom is sp^3 hybridized.[14] Steric hindrance and electrostatic repulsion may distort this bond-angle symmetry if large and/or dissimilar aryl (alkyl) groups are involved.

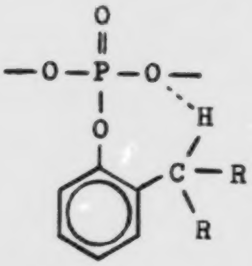
For ease of presentation and clarity, it is usual to represent the structure of the esters in two-dimensional form:

e.g.



where R_1, R_2 and R_3 may be alkyl groups or hydrogen. This type of representation makes it easier to depict the structure of reaction intermediates which may be involved in chemical reactions.

The toxicity of TAP/AAPs is closely related to their structure. The presence of an alpha-hydrogen on an ortho-substituted alkyl group is indicative of a TAP/AAP with neurotoxic potential. It is the spatial proximity of the alpha-hydrogen to the adjacent P-O-C ester linkage:



which permits the formation of a cyclic neurotoxic metabolite (a cyclic saligenin). The effect of structure on toxicity is discussed in Section 5.3.

3.2.2 Possible Combinations of Triaryl/alkyl Phosphates

Henschler pointed out that when a TAP is prepared by the phosphorylation of a mixture of phenols a number of triesters of phosphoric acid will be formed.[15] In general, if three or more phenols are used, there will be three types of triesters formed:

a) mixed esters in which the three hydrogen atoms of phosphoric acid are replaced with different phenols,

b) mixed esters with two identical and one different phenol, and

c) esters in which all three hydrogens are replaced with identical phenols.

Table 3-1 shows the number of ester combinations possible with different numbers of phenols present in the starting material. The relative amounts of each ester will, of course, depend on the concentrations of each phenol present, and also on the preparation conditions.

There are three isomeric cresols: o-, m-, and p-cresol. If tricresyl phosphate (TCP) were made from a mixture of all three isomers, 10 triester isomers could be formed. Another commonly used TAP is trixylyl phosphate which is made from the phosphorylation of xylol. There are six isomeric xylols (2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethyl phenol) which could result in the formation of 56 isomeric trixylyl phosphates.

Although cresylic acid feedstock -- a by-product of petroleum or coal tar distillation, consisting predominantly of phenol, methyl phenols (cresols) and dimethyl phenols (xylols) -- is no longer used in large quantities for the manufacture of TAPs (see Chapter 2), it was formerly the primary starting material for triaryl phosphate manufacture. Such a starting material could produce a mixture containing as many as 220 different triaryl phosphates.

As will be seen in subsequent sections of this report, awareness of the potential combinations of esters is pivotal in assessment of their environmental impact. The analytical chemist needs to be generally aware of the esters present in commercial TAPs in order

TABLE 3-1 Number of Different Triaryl Phosphates Possible from the Phosphorylation of a Given Mixture of Phenols*

No. of Phenols in Reactant Mixture	No. of Triesters That May Be Formed
1	1
2	4
3	10
4	20
5	35
6	56
7	84
8	120
9	165
10	220

---

* This table was developed from Henschler's discussion.[15]

to facilitate identification of the components of the mixture. Complementary to this, and probably of greater importance, the potential toxicity of TAPs (and AAPs) is closely related to the structure of individual triaryl phosphates. In at least one case (TCPs) demonstrated toxicity can vary by more than an order of magnitude between different structural isomers.[16]

3.2.3 Nomenclature

Van Wazer in his treatise, Phosphorus and Its Compounds, observed that "the naming of phosphorus compounds is in a very confused state, primarily because phosphorus chemistry is one of the oldest branches of this science".[14] The CRC Handbook of Physics and Chemistry names the acid first followed by the radical and the word ester: for example -- phosphoric acid, tri(2, 5-dimethyl phenyl) ester.[17] The International Union of Pure and Applied Chemistry also accepts this type of nomenclature.[18]

The above nomenclature can be clumsy to use and as Van Wazer points out "trivial names are probably quite satisfactory for this group, and there is no need -- at least at the present state of knowledge -- to spend effort on a systematic nomenclature for them".[14] It is common practice, therefore, to name TAP/AAPs as phosphates of the constituent radical groups. Alkyl groups are named first, followed by alkyl substituted phenyl groups and then by phenyl itself: e.g., tri-2,5-xylyl phosphate, 2-ethylhexyl diphenyl phosphate.

3.3 PHYSICAL CHARACTERISTICS

3.3.1 Intermolecular Bonding

The extent of intermolecular bonding is a determing factor in the physical characteristics of TAP/AAPs. In these compounds, the P=O bond in the phosphoryl group has a semipolar character.[27] This polarization enhances intermolecular bonding and will be reflected, for example, in the compounds' melting and boiling points, densities and viscosities.

Infrared spectroscopy has shown that the order of intermolecular hydrogen bonding ability of triphenyl and tricresyl phosphates to chlorohydrocarbon solvent molecules (chloroform, pentachloroethane, sym-tetrachloroethane and dichloromethane) is:[28]

$$(C_6H_5O)_3PO > (p\text{-}CH_3C_6H_4O)_3PO > (m\text{-}CH_3C_6H_4O)_3PO >$$

$$(o\text{-}CH_3C_6H_4O)_3PO.$$

3.3.2 Physical Properties of Pure Compounds

The physical properties of pure TAP/AAPs are not extensively characterized in the literature. The available values for melting points, boiling points, density and solubility characteristics are presented in Table 3-2. In the few instances where there was more than one published value for a particular compound, the source chosen was the one which appeared to be for the purest sample. In general the pure compounds are likely to be solids at room temperature. They distill at relatively high temperatures under reduced pressure -- at

TABLE 3-2 Physical Properties of Pure Triaryl/alkyl Phosphates

PHOSPHATE ESTER	M.W.	m.p. °C	b.p. °C	s.g.	Solubility									References
					w	al	eth	bz	to	hx	cl	ct	aa	
TRIPHENYL PHOSPHATE	326.3	50 to 51	245 @1460 Pa	1.206_4^{50}	i	ms	vs	vs			vs	vs		19
TRICRESYL PHOSPHATES	368.4													
$(o\text{-cresyl})_3$		11	410* 283 - 5 @2670 Pa	1.196_4^{20}	i	vs	vs		vs			vs	vs	19
$(m\text{-cresyl})_3$		25 to 26	260 @2000 Pa	1.150^{25}	i	ss	ms		vs			vs	ms	19
$(p\text{-cresyl})_3$		77 to 78	244 @467 Pa	1.247^{25}		ss	ss	ms				ms	ms	19
TRIXYLYL PHOSPHATES	410.5													
$(2,3\text{-dimethylphenyl})_3$		61												20
$(2,4\text{-dimethylphenyl})_3$			232 - 5	1.142_4^{28}	i			ms		ms				19
$(2,5\text{-dimethylphenyl})_3$		78.6 to 81	260 - 5 @1070 Pa	1.197^{25}	i	ss	ms	ms	ms	ss		ms		19
$(2,6\text{-dimethylphenyl})_3$		136 to 8	262 - 4 @800 Pa		i	ss		ms		ss				19
$(3,4\text{-dimethylphenyl})_3$		71.5 to 2.5	260 - 3 @930 Pa		i	ss		ms		ss				19
$(3,5\text{-dimethylphenyl})_3$		46	290 @1330 Pa											19
CRESYL/PHENYL PHOSPHATES														
(o-cresyl diphenyl)	340.3		255 - 65 @1600 Pa											21
(di-p-cresyl phenyl)	354.3	54												22
TRI-ISOPROPYLPHENYL PHOSPHATES	452.5													
$(o\text{-isopropylphenyl})_3$		34												20
$(m\text{-isopropylphenyl})_3$		-50												20
$(p\text{-isopropylphenyl})_3$		-38												20
BUTYLPHENYL/PHENYL PHOSPHATES														
$(p\text{-t-butylphenyl})_3$	494.6	101	315 - 7 @530 Pa											23
(di-t-butylphenyl phenyl)	438.5	41	281 @730 Pa											20,23
(t-butylphenyl diphenyl)	382.4	31	261 @800 Pa											20,23
ALKYL/ARYL PHOSPHATES														
(2-ethylhexyl diphenyl)	362.4		232 @670 Pa	1.09^{25}										24
(dibutyl phenyl)	286.3		200 @2670 Pa											25
(butyl diphenyl)	306.3		194 - 200 @670 Pa											26

* boiling point at atmospheric pressure with decomposition

i insoluble

ss slightly soluble

ms moderately soluble

vs very soluble

w water
al ethanol
eth diethyl ether
bz benzene
to toluene
hx hexane
cl chloroform
ct carbon tetrachloride
aa acetic acid

atmospheric pressure decomposition will probably occur before the boiling point is reached. All the phosphates are more dense than water. They are essentially insoluble in water but are soluble in a wide variety of organic solvents.

An indication of the magnitude of variations in physical properties between different isomeric forms of a compound may be gained from the boiling points of tricresyl phosphate structural isomers presented in Table 3-3. It may be seen that there is a range in boiling points (at about 130 Pa) of about 30° C.

3.3.3 Physical Properties of Commercial Products

The physical properties of some commercial TAP/AAPs are presented in Table 3-4. The products are (with the probable exception of TPP) mixtures of phosphate esters and are listed with respect to their major chemical constituent. The supplying companies (e.g., Ciba-Geigy - Reofos,TM Reolube;TM Monsanto - Santicizer,TM Pydraul;TM Stauffer - Phosflex,TM FyrquelTM) offer a whole range of substances under their trade names (only some of which would contain TAP/AAPs as their major component) with the composition tailored to give specific physical and chemical properties. The individual compositions of these mixtures are proprietary and were unavailable.

It will be noted that, in contrast to pure compounds, most of the commercial products are liquids at room temperature. This is a consequence of their being mixtures, with the majority of molecules being unsymmetrical phosphate esters. This liquid character is important and desirable in commercial usage. For example, pure

TABLE 3-3 Boiling Points of Tricresyl Phosphate Isomers

Isomer	Klimmer and Schunk[16] (reduced pressure)*	Bondy *et al*[29] (at 130 Pa)
o, o, o	196.5 to 196 °C	209 to 207 °C
o, o, m	199 to 198.5	
o, m, m	204.5 to 204	
o, o, p	205 to 204.5	
o, p, p	209 to 208.5	225.5 to 223.5
o, m, p	210 to 209.5	
m, m, m		226 to 224
p, p, p		238.5 to 236.5

* These data were obtained from information sent to us by the International Register of Potentially Toxic Chemicals, Geneva. It was not possible to determine the pressure at which this series of boiling points was obtained, but judging from the values the pressure would likely have been of the order of 130 Pa.

TABLE 3-4 Physical Properties of Some Commercial Triaryl/alkyl Phosphates

Major Component	Trade Name	m. p. ** °C	b. p. °C	Specific Gravity	Solubility in H_2O % (°C)	Appearance
Triphenyl phosphate	TPP (Monsanto)	49	238 @ 130 Pa	1.268^{60}_{20}	0.001 (34)	White flakes
Tricresyl phosphate	TCP (Monsanto)	-35	420 @ 101 kPa	1.162^{25}_{25}	0.002 (85)	Clear, colourless to light yellow, oily liquid
	Phosflex 179C (Stauffer)	-30		1.167^{20}_{20}	trace	Clear, transparent liquid
Trixylyl phosphate	Phosflex 179A/EG (Stauffer)	-18		1.143^{20}_{20}	trace	Clear, colourless liquid
Cresyl diphenyl phosphate	Phosflex 112 (Stauffer)	-37		1.208^{20}_{20}	trace	
	Santicizer 140 (Monsanto)	-37	390 @ 101 kPa	1.208^{25}_{25}	0.005 (25)	
t-Butylphenyl diphenyl phosphate	Santicizer 154 (Monsanto)	-20	250 @ 130 Pa	1.180^{25}_{25}	0.001 (25)	Clear, mobile liquid
2-Ethylhexyl diphenyl phosphate	Santicizer 141 (Monsanto)	-54	239* @ 130 Pa	1.090^{25}_{25}	0.003 (25)	Clear, oily liquid
Isodecyl diphenyl phosphate	Santicizer 148 (Monsanto)	-60	245* @ 130 Pa	1.074^{25}_{25}	0.003 (25)	Clear, oily liquid

* Signifies thermal decomposition

** These substances often do not have "true" melting points. The figures quoted are usually referred to in trade literature as "crystallization point" or "pour point".

SOURCE: The information presented in this table was obtained from company technical data sheets.

triaryl phosphates used to plasticize PVC tend to crystallize after incorporation in the plastic and thus lose their effectiveness on aging.[20]

Commercial TAP/AAPs are highly viscous liquids at room temperature. Their viscosity decreases markedly as the temperature is raised. This effect is illustrated by the viscosity characteristics of Fyrquel 220 (a triaryl phosphate mixture manufactured by Stauffer Chemical Company) and is typical of the class of compounds. At 10° C Fyrquel 220 has a viscosity of 499.6 centistokes which decreases to 5.5 centistokes at 99° C.[30]

In most applications, the choice of a plasticizer is made upon the physical characteristics (e.g., liquid viscosity, low temperature flexibility) of the product rather than on its chemical composition. Although, as outlined in the following section, the characteristics of the fire retarded plastic are also related to the chemical nature of the TAP/AAP plasticizer.

3.4 CHEMICAL CHARACTERISTICS

3.4.1 Manufacture

Industry differentiates between phosphate esters produced from cresylic acid (a complex mixture of phenol, cresols and xylols) and those from mixtures of known phenols (and alcohols). The former are designated "natural" TAPs and the latter are known as "synthetic" TAPs. The basic production method is, however, similar. Most TAP/AAPs currently on the market are of the synthetic variety.

3.4.1.1 Triaryl phosphates: Chadwick and Watt describe a number of methods for the preparation of triaryl phosphates.[31] However, manufacturing processes currently in use involve the reaction of phenols with phosphorus oxychloride in the presence of a metal chloride catalyst ($AlCl_3$, $ZnCl_2$):[8]

$$3ArOH + POCl_3 \xrightarrow[150\ to\ 300^\circ C]{catalyst} (ArO)_3PO + 3HCl$$

For esters produced from a single phenol, a slight excess of the phenol is used so as to favour complete esterification. In reactions involving mixed phenols, the individual compounds are added in stoichiometric quantities that correspond to the composition of the major product. For example, if cresyl diphenyl phosphate is the desired product, the reaction mixture would contain one part cresol to two parts phenol. As mentioned earlier, the final product would contain all four possible esters (i.e., triphenyl phosphate, cresyl diphenyl phosphate, dicresyl phenyl phosphate and tricresyl phosphate) with cresyl diphenyl and triphenyl phosphates predominating.

After the reaction has proceeded to completion (in six to nine hours at 200° C) the unreacted phenolic material is removed by distillation at reduced pressure (6.7 kPa). The pressure is then reduced to about 0.4 kPa to permit distillation of the TAP.[8] Final purification steps may employ washing with dilute sodium hydroxide solution and water to remove traces of organic and hydrochloric acids, treatment with dilute permanganate solution to improve colour and oxidation stability of the product, dehydration by heating under reduced pressure, bleaching with activated carbon and/or diatomaceous earth, and finally filtration.[31]

It is possible that some mixed triaryl phosphates (such as butylphenyl phenyl phosphates) are produced by successive addition of the two phenols rather than from a mixture in a one step process. This would enable a manufacturer to more closely control the identity of the individual ester components in the final product. The two processes would be carried out in the same reactor. In the first stage only one phenol would be present and the reaction temperature would be held to about 100° C; under these conditions predominantly aryl and diaryl phosphoryl chlorides would be formed. After completion of the preliminary reaction the second phenol would be added to the reactor and the temperature raised to complete the phosphorylation.[31]

3.4.1.2 Tri-(alkyl aryl) phosphates: Slightly different conditions are necessary when alcohols are phosphorylated because the alcohol ester linkage is susceptible to cleavage by the hydrogen chloride liberated during the reaction. One technique, used in the production of 2-ethylhexyl diphenyl phosphate, involves preparation of an alkyl phosphoryl dichloride by reaction of equimolar portions of the alcohol and phosphorus oxychloride under low temperature (15° C) conditions, followed by esterification of the dichloride with sodium phenate at temperatures below 5° C.[8,24]

Alternatively, an aryl or diaryl phosphoryl chloride can be formed first using the conditions described above in Section 3.4.1.1, followed by cooling of the reaction mixture to below room temperature. The alcohol is then added slightly in excess of stoichiometric quantities and the hydrogen chloride by-product is removed during the reaction to avoid cleavage of the alcohol ester bond.[8]

3.4.2 The Chemical Bases for Commercial Application of Triaryl/alkyl Phosphates

The commercial applications of TAP/AAPs are based upon their lubrication and fire retardant properties. These applications are varied. In plastics, the esters serve both as plasticizers and fire retardants. As oil additives, their primary function is lubrication and in hydraulic fluids both flame retardancy and lubricity are the desirable characteristics.

3.4.2.1 Fire retardancy: Two classes of combustion in plastic materials are recognized: flaming, which involves oxidation of gaseous products and solid phase combustion, which is termed glowing. Organophosphorus fire retardants (of which TAP/AAPs are an example) thermally degrade to produce condensed phosphoric acids. They are successful both in inhibiting volatilization of flammable solids (such as plastics) by char formation and by acting in the gas phase to remove the free radical carriers of combustion reactions.[32]

In plastics, it is known that the hydrogen ions of the condensed phosphoric acids catalyze the thermal degradation of the overall polymeric mass to give a preponderance of char and a minimum of volatile decomposition products, the oxidation of which supports flaming. The same mechanism acts to prevent glow formation in the solid phase.[2]

3.4.2.2 Plasticization: A plasticizer may be defined as a material incorporated in a plastic or elastomer to increase its flexibility, workability or distensibility. The mechanism of plasticization may be viewed by considering a plastic as a gel and by attributing the action of the plasticizer to the reduction of the extent of gel structure that would otherwise exist. This gel theory postulates that brittleness and stiffness in an unplasticized resinous mass are due to a closely packed three-dimensional network structure formed by secondary bonding between various attractive centres on the macromolecules. The action of the plasticizer on a resinous substance having many points of intermolecular interaction is to solvate or mask these points and thereby essentially eliminate them as potential sites for interaction with neighbouring polymer molcules. Such a mechanism may be considered to be a molecular-scale lubrication.[2]

The effectiveness of alkyl substituted triaryl phosphates as PVC plasticizers has been assessed by Duke.[20] It was shown that the most important factors are the position of the alkyl substituent on the benzene ring and the extent of concurrent polysubstitution on the aryl groups. These factors correlated with physical properties such as plasticizer efficiency (especially low temperature flexibility) and liquid viscosity properties. They also had a bearing on chemically controlled properties of the PVC, such as colour stability and stability to light. Meta-substitution, at least with methyl, ethyl or isopropyl groups, had very favourable effects on low temperature flexibilities. Significant meta-isomer content, however, resulted in severe deterioration of the colour stabilities and compatabilities of PVC compositions. Duke concluded that the preferred substituent type, taking all factors into consideration, is orthoisopropyl, accompanied by substantial levels of unsubstituted phenyl groups and a small content of polysubstitution.

3.4.2.3 Lubrication: Organophosphorus compounds are one class of compound added to improve the performance of hydrocarbon lubricating oils. Some proprietary compositions contain around 4% phosphorus (measured as the element).[2] Triaryl phosphates are one class of organophosphorus compounds used for this purpose.

Organic phosphorus compounds impart antiwear properties, corrosion inhibition and some extreme pressure characteristics. Modern gears transmit such high forces that simple hydrocarbon lubricants may be completely extruded from between the gear teeth so that, as the gears mesh, they are essentially non-lubricated. Phosphorus additivies build up a hard, highly polished, phosphorus-containing surface on the gears, which prevents direct metal-to-metal contact and through the effect of residual organic ligands, tightly holds the hydrocarbon lubricant through chemisorption.[2]

Completely synthetic lubricants have been developed for special uses such as in jet-aircaft engines. To impart extreme-pressure characteristics to the synthetic lubricants, a small percentage of a phosphorus ester, such as tricresyl phosphate, is added.[2] It is suggested that tricresyl phosphate is adsorbed on the metal surface and decomposes to give acid phosphates, which react with the metal surface to give metal organo-phosphates.[33]

3.4.2.4 Hydraulic fluids: Fire resistance may be extremely desirable in fluids used to actuate hydraulic mechanisms -- as in aircraft, die-casting machines, and turbine governor systems. The fluids in these systems are piped at very high pressures. As an example, the hydraulic control mechanisms of large steam turbines used for electricity generation operate at pressures of between 7,000 and 12,400 kPa.[34] A rupture in the system could result in a flammable liquid being sprayed onto a hot surface, producing a serious fire hazard. Use of a fire-resistant phosphorus-based fluid avoids this problem. The exact composition of such hydraulic fluids is generally proprietary information. However, some of these fluids are based on orthophosphate esters. These esters impart not only fire-resistance but also lubricity to the formulation.[2]

3.4.3 Degradative Chemistry

3.4.3.1 Oxidation: Standard texts on phosphorus compounds do not mention oxidation as a typical reaction of TAP/AAPs. The Midwest Research Institute suggests that the strongest oxidizing agent these materials are likely to contact in the environment is chlorine or the hypochlorite ion.[8] The Institute, citing an unpublished opinion, suggest the slight possibility of chlorination of the aryl group in the presence of chlorine in aqueous solution but suggest also that oxidative cleavage of the ester bond would not occur.

3.4.3.2 Photolysis: One study of the photolysis of triaryl phosphates has been reported.[35,36] Three triaryl esters (triphenyl, tri-p-tertiary-butylphenyl and tri-p-cresyl phosphates) were irradiated, as 0.02M solutions in ethanol, with a medium pressure mercury arc lamp. The major characteristic of the photolysis was the formation of biaryl compounds:

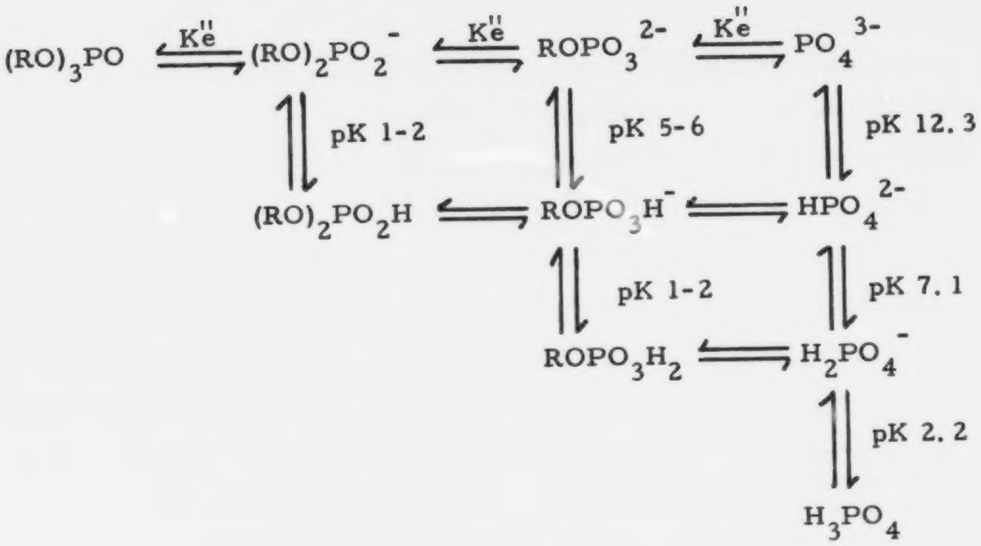
$$(ArO)_3PO \xrightarrow[C_2H_5OH]{h\nu} Ar\text{-}Ar + ArOPO_3H_2$$

Triphenyl phosphate was the least reactive of the three triaryl phosphates investigated, producing only 2% biphenyl after 5 hours irradiation compared with 51% 4,4'-dibutylbiphenyl from tri-p-butylphenyl phosphate and 35-51% 4,4'-dimethylbiphenyl from tri-p-cresyl phosphate after the same length of irradiation. When an equimolar mixture of triphenyl and tricresyl phosphates was irradiated, however, the yield of biphenyl increased to 21%, suggesting some intermolecular energy transfer. The authors concluded that the formation of biaryl products is an intramolecular reaction which occurs either in a concerted fashion or between fragments very tightly contained within a solvent cage.

The major UV emission from the medium pressure mercury arc lamp is the 253.7 nm line. There are other emission lines in the UV region and an intense line in the visible region at 435.8 nm.[17] But the spectra of triaryl phosphates show major absorption peaks only in the 260-275 nm region,[19] and therefore the photolysis reactions described above are a result of UV irradiation.

3.4.3.3 Hydrolysis: Common and typical reactions of organic phosphate esters involve attack by nucleophiles on either the phosphorus atom of the phosphoryl group or on the carbon atom of the ester linkage.[37,38] In aqueous media the nucleophiles would be either the hydroxyl ion (a "hard" nucleophile) or the water molecule (a "soft" nucleophile).[38]

The hydrolysis of phosphoric acid triesters can involve complex equilibria between neutral molecules, mono-anions, di-anions and the orthophosphate ion:[8]



$$\begin{tikzcd}
(RO)_3PO \arrow[r, shift left, leftarrow, "K_e''"] \arrow[r, shift right, rightarrow] & (RO)_2PO_2^- \arrow[r, shift left, leftarrow, "K_e''"] \arrow[r, shift right, rightarrow] \arrow[d, shift left, leftarrow] \arrow[d, shift right, rightarrow, "\mathrm{p}K\ 1\text{-}2"'] & ROPO_3^{2-} \arrow[r, shift left, leftarrow, "K_e''"] \arrow[r, shift right, rightarrow] \arrow[d, shift left, leftarrow, "\mathrm{p}K\ 5\text{-}6"] \arrow[d, shift right, rightarrow] & PO_4^{3-} \arrow[d, shift left, leftarrow, "\mathrm{p}K\ 12.3"] \arrow[d, shift right, rightarrow] \\
& (RO)_2PO_2H \arrow[r, shift left, leftarrow] \arrow[r, shift right, rightarrow] & ROPO_3H^- \arrow[r, shift left, leftarrow] \arrow[r, shift right, rightarrow] \arrow[d, shift left, leftarrow, "\mathrm{p}K\ 1\text{-}2"] \arrow[d, shift right, rightarrow] & HPO_4^{2-} \arrow[d, shift left, leftarrow, "\mathrm{p}K\ 7.1"] \arrow[d, shift right, rightarrow] \\
& & ROPO_3H_2 \arrow[r, shift left, leftarrow] \arrow[r, shift right, rightarrow] & H_2PO_4^- \arrow[d, shift left, leftarrow, "\mathrm{p}K\ 2.2"] \arrow[d, shift right, rightarrow] \\
& & & H_3PO_4
\end{tikzcd}$$

where R may be an aryl or alkyl group.

The experimental conditions under which such reactions are studied are usually significantly different from those that would be found in the environment. (Most studies have been carried out at 100° C and often with esters which have an electron withdrawing group, such as NO_2, on the phenyl group -- these conditions give sufficiently fast reactions for laboratory study.) However, they do provide a general guide to what may occur under environmental conditions.

Isotope exchange studies have shown that nucleophilic attack on triaryl phosphates occurs at the phosphorus atom and involves cleavage of the O-P bond.[39] The study investigated triphenyl phosphate which, because of its insolubility in water, was dissolved in a 60% dioxan-water mixture. The triesters of phosphoric acid are readily hydrolysed in basic solution in comparison to the corresponding diesters.[37] An estimate made of the relative effectiveness of OH^- and H_2O as nucleophiles showed that, towards the phosphorus atom, the hydroxide ion is a more reactive nucleophile than water by a factor of about 10^8.[39]

Except at low pH, disubstituted phosphate esters exist as anions in water, and except for five-membered cyclic phosphates and diaryl phosphates which contain strongly electron attracting substituents, they are relatively unreactive toward anionic nucleophiles.[38] At pH values below 7, the principal bond broken during hydrolysis is the O-P bond. In alkaline solution, however, the rates for nucleophilic attack by OH^- at carbon and phosphorus are about equal.[40] Reaction rates, where they can be compared under similar conditions, are considerably slower than those of triesters.

The hydrolysis of mono-substituted aryl phosphates is acid catalyzed and shows a rate maximum at about pH 4. The rates of reaction are much faster than for the corresponding diesters. Phenyl dihydrogenphosphate, for example, hydrolyses at 100° C and pH 4 about 9×10^4 times faster than diphenyl phosphate. The difference is still considerable at pH 7.5 (3×10^3). The hydrolysis of phenyl dihydrogenphosphate is faster than that of p-cresyl dihydrogenphosphate, with the difference becoming more marked as the pH increases.[41]

The relative hydrolysis rates of the three ester groups are: tri $>$ di $<$ mono. In most cases, nucleophilic attack occurs at the phosphorus atom leading to O-P bond cleavage, although under certain circumstances C-O bond fission also occurs. The hydrolysis of TAP/AAPs will occur more readily in alkaline solution than under neutral or acidic conditions.

3.4.3.4 Summary: The common mechanisms for chemical degradation under environmental conditions are oxidation, photolysis and hydrolysis. With the exception of hydrolysis, however, TAP/AAPs are likely to be chemically unreactive in the environment. Reactions under simulated or actual environmental conditions, which may include microbial action, are discussed in Section 4.5.

3.5 ANALYTICAL TECHNIQUES

The method of choice for analysis of commercial TAP/AAPs is gas chromatography as it is capable of identifying and measuring the individual components. With appropriate concentration techniques gas chromatography is able to measure concentrations of TAP/AAPs in the parts per billion and even the parts per trillion ranges necessary for environmental samples. However, adequate methods to accomplish this have only recently been developed and the published data are sparse.

Secondary and often non-specific methods have been in use for a greater time period. These techniques serve primarily as methods for detection of the presence of TAP/AAPs in a given sample. The absence of phosphorus compounds other than the required TAP/AAPs in the sample is often a prerequisite for such analyses to have practical meaning.

3.5.1 Chromatography

The earlier gas chromatographic (GC) methods relied upon degradation of the TAP/AAP sample, commonly by exhaustive hydrolysis to yield its constituent phenols and alcohols. More recently, techniques derived from advances made in analysis of organophosphorus pesticide residues have been developed which permit identification of unchanged individual constituents of the TAP/AAP mixtures.

3.5.1.1 Non-degradative GC methods: Deo and Howard developed a gas-liquid chromatographic/mass spectrometric method to analyse commercial TAP/AAPs.[42] Identification of the chromatographic peaks was made by comparing retention times of known TAP/AAP standards and/or using the m/e value of the parent ion from the mass spectrometer detector. The results the authors obtained are presented, together with results from other studies [43,44] in Table 3-5. It is worth pointing out that even with such a comparatively sophisticated technique care has to be exercised in identification of the components. In their analysis of Fyrquel GT, Deo and Howard identified xylyl dicresyl phosphate (m/e 382) and tri-(C_3-phenyl) phosphate (m/e 438) as the major components of this functional fluid. However, the fluid's manufacturer, Stauffer Chemical Co., indicated that the only phenols used in the manufacture of Fyrquel GT were tertiary butylphenols and phenol with a small amount of cresol.[45] Accordingly the two major constituents identified by Deo and Howard are almost certainly t-butylphenyl diphenyl phosphate (m/e 382) and di-t-butylphenyl phenyl phosphate (m/e 438).

The chromatographic technique used by Deo and Howard was adapted from methods developed for the analysis of organophosphorus pesticide residues and employed a 1.83 m column packed with 3% OV-101 on 80-100 mesh Chromosorb W, coupled with a flame photometric

TABLE 3-5 Composition of Some Commercial Triaryl Phosphates

PLASTICIZERS	%	FUNCTIONAL FLUIDS	%
KRONITEX TCP[42]		PYDRAUL 50E[42]	
tri-m-cresyl phosphate	20.7	triphenyl phosphate	19.0 (35)
di-m-cresyl p-cresyl phosphate	38.8	p-nonylphenyl diphenyl phosphate	52.8 (40)
di-p-cresyl m-cresyl phosphate	30.4	4-cumylphenyl diphenyl phosphate	24.0 (22)
dicresyl xylyl phosphates	9.2	unidentified hydrocarbons	3.8 (3)
SANTICIZER - 140[42]		PYDRAUL 115E[43]	
triphenyl phosphate	14.7	triphenyl phosphate	7
m-cresyl diphenyl phosphate	18.6	nonylphenyl diphenyl phosphate	29
p-cresyl diphenyl phosphate	14.4	cumylphenyl diphenyl phosphate	62
dicresyl phenyl phosphate	29.4		
tricresyl phosphates	19.4		
PHOSFLEX 41-P[42]		FYRQUEL GT[42]	
triphenyl phosphate	11.9	triphenyl phosphate	19.2
m-cresyl diphenyl phosphate	2.1	m-cresyl diphenyl phosphate	2.1
tricresyl phosphates	40.8	dicresyl phenyl phosphate	3.2
trixylyl phosphates	9.4	*xylyl dicresyl phosphates	36.2
tri-(C_3-phenyl) phosphates	28.7	**tri-(C_3-phenyl) phosphates	37.1
unidentified peaks	6.9		

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* This should probably be t-butylphenyl diphenyl phosphate -- see text.

** This should probably be di-t-butylphenyl phenyl phosphate -- see text.

( ) Values reported by Lombardo and Egry[44] and Mayer et al[43].

detector equipped with a 526 nm filter (nitrogen-phosphorus sensitive detector). Similar equipment has been used by other researchers who, in addition, also employed OV-17 as the liquid phase.[44,46] A similar method using a silicone-fluid liquid phase, OV-210, and a flame ionization detector, was used by Bloom to separate and quantitate triphenyl phosphate, 2-ethylhexyl diphenyl phosphate and tricresyl phosphates (o, m, and p-isomers).[47] Detection limits varied from 5 to 30 ng.

3.5.1.2 Degradative GC methods: A method developed by Murray to analyze triaryl phosphates extracted from water and fish tissue samples, involved reaction of the sample with alcoholic potassium hydroxide and analysis of the hydrolysis products by gas chromatography.[48] The alcoholic KOH mixture was placed in sealed ampoules and autoclaved for 90 minutes. This procedure hydrolysed the phosphate esters to their component phenols. After dilution of the hydrolysate with water, acidification with hydrochloric acid and extraction with chloroform the phenols were converted to their trimethylsilyl derivatives. These derivatives were then analyzed gas chromatographically on a column packed with 5% IMOL (a commercial triaryl phosphate) on Chromosorb W coupled to a flame ionization detector. This hydrolysis procedure essentially determines the composition of the phenolic mixture used to produce the triaryl phosphates but cannot determine ratios of the individual TAPs in the commercial mixture.

This same technique was used by Hunter to characterize Fyrquel EHC, a TAP control fluid used in steam turbine electricity generators at Ontario Hydro's Bruce Generating Station.[49] The results obtained are shown in Table 3-6, and may be compared with a typical analysis of the cresylic acid used by Stauffer Chemical Company to manufacture the functional fluid. It will be seen that the two sets of data are in close agreement as to total xylol content (87.8% analyzed by Ontario Hydro and 86.4% for a typical cresylic acid).

Boyden and Decon determined traces of tetra-aryl pyrophosphates and diaryl phosphochloridates as impurities in tricresyl phosphate.[50] These authors converted tetracresyl phosphates to dicresyl methyl phosphate by treatment with methanol. Dicresyl phosphochloridate was converted to t-butyl chloride and dicresyl phosphate by treatment with t-butanol. These solvolysis products were analyzed using a 3% SE 30 silicone oil liquid phase.

3.5.1.3 High pressure liquid chromatography: The Midwest Research Institute report one (unpublished) method, based on reverse-phase partition gradient elution using a high-pressure liquid chromatograph (HPLC) developed by the FMC corporation.[8] The method was used on samples of organophosphates concentrated from river water and sewage by vacuum distillation and taken up in acetonitrile. The acetonitrile extract was analyzed by an HPLC fitted with a UV (220 nm) detector to indicate the presence of triaryl/alkyl phosphates.

3.5.1.4 Thin-layer chromatography: Thin-layer chromatography (TLC) has been used by some investigators to identify trace quantities of triaryl phosphates in a variety of media.

Rapaport and Lebedinskaya used TLC to determine trace quantities of tri-o-cresyl phosphate in wines and from samples of protective

TABLE 3-6 Composition of Phenols Used to Manufacture Fyrquel EHC

Ontario Hydro's Analysis[49]		*Typical Phenolic Composition of Cresylic Acid Used in Manufacture[45]		
phenol	0. 1%	phenol	0. 1%	(0. 1)
m-cresol	7. 2	o-cresol	0. 1	(0. 1)
p-cresol	4. 9	m- & p-cresol	8. 8	(11. 9)
2, 5-xylol	20. 0	o-ethylphenol	0. 8	(1. 1)
2,4- & 3, 5-xylols	29. 9	2, 6-xylol	0. 1	(0. 1)
2, 3-xylol	22. 7	2, 4- & 2, 5-xylols	25. 0	(33. 8)
3, 4-xylol	15. 2	mixed xylols (primary 2, 3-)	36. 8	(49. 7)
		3, 4- & 3, 5-xylols	2. 1	(2. 8)
		compounds with 8 carbon atoms	0. 2	(0. 3)

* It should be noted that cresylic acids contain non-phenolic constituents (to 26% in the case shown). The percentage of each phenolic constituent relative to the total phenolic content is shown in parentheses.

coverings of winebarrels.[51] The samples were extracted with hexane and phenolic impurities removed by shaking with 1% aqueous sodium hydroxide. The hexane was then evaporated, the residue taken up in diethyl ether and the resulting solution spotted onto a plate supporting a thin layer of alumina fixed by gypsum and starch. The chromatogram was developed with a 20:1 benzene/chloroform eluant. After drying, the plate was treated with 15% aqueous sodium hydroxide and the resulting cresol was diazotized with an acidified p-nitroaniline/sodium nitrite solution. A red-brown spot on a yellow background indicated the position of the tri-o-cresyl phosphate. Sensitivities of 0.02 to 0.05 mg/L TOCP in wine samples and 2.5 µg/g TOCP in covering material samples were reported.

Sengupta et al used TLC to detect tricresyl phosphate in edible oils.[52] The oil was saponified with alcoholic potassium hydroxide and the resultant mixture was spotted onto silica gel plates. Development of the chromatogram was accomplished using a 90:10 iso-octane/ethyl acetate eluant. Tricresyl phosphate was indicated as a red spot by first spraying the plate with 1.5N alcoholic potassium hydroxide, heating it to 60° C and then spraying with acidified p-nitroaniline/sodium nitrite solution. Similar techniques have been reported which enabled identification of tri-o-cresyl and tri-p-cresyl phosphates in mustard oils.[53]

3.5.2 Spectroscopy

Ultraviolet and infrared spectroscopy have been used to identify triaryl phosphates in samples of edible oils, in workplace air and in soil samples. Nuclear magnetic resonance (^{31}P) spectroscopy has been used as an aid to identify triaryl phosphates in mixtures of organophosphorus compounds.

3.5.2.1 Ultraviolet spectroscopy: Pundlik and Meghal suggest the use of ultraviolet absorption at 262 nm to detect tricresyl phosphate extracted with 80% ethanol from edible oils.[54] The authors demonstrated that, for TCP, absorption at 262 nm obeys Beers Law.

3.5.2.2 Infrared spectroscopy: Infrared spectroscopy was used to aid the detection and measurement of a commercial triaryl phosphate functional fluid in the workplace air at Ontario Hydro's Bruce Generating Station.[55,56] The presence of a triaryl phosphate functional fluid in soil samples obtained after a spill at a Trans Canada Pipelines compressor station near Barrie, Ontario, was detected using IR spectroscopy.[57]

3.5.2.3 NMR spectroscopy: Gurley and Ritchey have developed a technique for determining organophosphates, phosphonates and thiophosphates in solution based on ^{31}P Fourier transform NMR spectroscopy.[58] Organophosphates when dissolved in chloroform, ethyl acetate, acetonitrile or methanol, exhibit characteristic spin-lattice relaxation times (approximately 10 to 20 seconds) in the presence of tris-(1,1,1,2,2,2,3,3-octafluoro-7-methyl-4,6-octanedionato) gadolinium (III). In a solution of parathion, malathion, triethyl thiophosphate and triphenyl phosphate at concentrations ranging from 30 to 100 ppm, it was reported that each compound could be easily determined using a 25 minute scan.

3.5.3 Methods Used in Analysis of Environmental Samples

The basic analytical techniques outlined in the preceding sections can be used in the analysis of environmental samples for TAP/AAPs. Usually, such analyses employ some form of concentration technique. Only gas chromatography has the demonstrated ability of measuring the many individual components of commercial TAP/AAP mixtures.

3.5.3.1 Air sampling: Both Tenax traps and particulate filters have been used in an attempt to collect TAP/AAPs in ambient air in the vicinity of U.S. facilities involved in the manufacture or use of aryl phosphates.[59] Three cubic metres of air were either passed through a trap containing 3 g Tenax or a particulate filter. The collection media were extracted with 80 mL heptane in a Soxhlet extractor. The heptane was evaporated to 200 μL and injected into a gas chromatograph for analysis. A detection limit for TAP/AAPs of 0.3 ppb in air was reported.

A similar, and as yet unpublished study by the U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory - Las Vegas, has been reported by the Midwest Research Institute.[8] This EPA-Las Vegas laboratory study used high volume air filter pads and activated carbon filters to sample ambient air. The filter pads were extracted with di-isopropyl ether and concentrated by evaporation before injection into a gas chromatograph for analysis. The carbon filters were Soxhlet extracted with benzene and the benzene extractant was evaporated to dryness. The residue was taken up in di-isopropyl ether for chromatographic analysis. The been used as an aid to identify triaryl phosphates in mixtures of organophosphorus compounds.

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A technique was developed by Ontario Hydro to measure triaryl phosphate functional fluid in workplace air.[55, 56] A sample train consisting of five 500 mL impingers, cooled to -75° C, through which air was drawn was the collector for organic components. The first and last impingers were empty and the middle three contained n-heptane. The first impinger trapped atmospheric moisture and the last impinger acted as a cryogenic trap for material passing through the first four. The heptane was evaporated to dryness and the residue was treated with a mixture of sulphuric and nitric acids (to hydrolyse the TAPs to phosphoric acid). The resulting solution was analyzed for phosphorus content by the stannous chloride/ammonium molybdate colorimetric method detailed in Standard Methods for the Examination of Water and Wastewater, 13th edition, of the American Public Health Association. In calibration tests, using the functional fluid, the recovery was found to be better than 95%. The colorimetric method measures total phosphorus content and is not specific for TAPs. Infrared spectroscopy was used to confirm that the functional fluid was the source of the phosphorus measured. In this spectroscopic analysis the heptane from the sampling train was evaporated to dryness and the residue ground with potassium bromide. The KBr mixture was compressed into a disc and its infrared spectrum was recorded between 3 μm and 16 μm. The functional fluid showed prominent absorption peaks at 7. 6 and 10. 3 μm and gave an estimated detection limit for the TAP fluid of 0. 02 mg.

3.5.3.2 Water sampling: A method to analyse drinking water for organophosphorus compounds (including triaryl phosphates) was developed by LeBel and co-workers.[46,60] The method passes a water sample (of up to 200 L) through a macroreticular resin (Amberlite XAD-2) column. The resin adsorbs organic components present in the water. After vacuum drying, the column was eluted with 300 mL acetone:hexane (15:85). The eluate, after drying with anhydrous sodium sulphate, was concentrated to about 1 mL in a flash evaporator. A 2 µL aliquot was then injected into a gas chromatograph for analysis. Detection and quantitation of triphenyl, tricresyl and 2-ethylhexyl diphenyl phosphates at sub-nanogram per litre levels were reported.

Solvent extraction methods have been employed in the analysis of natural waters for TAP/AAPs. Chloroform[48] and methylene chloride[44,59] have been used as extractants. In all cases the extractant was concentrated by evaporation prior to injection of an aliquot into a chromatograph for analysis.

3.5.3.3 Soil and sediment sampling: A technique for analysing soil samples for TAP/AAPs by extraction with methylene chloride has been described by Clarke.[59] A 50 g soil sample was slurried with 100 mL of methylene chloride to which an internal standard (10 µg tris-butoxyethyl phosphate) had been added. The slurry was shaken for 30 minutes and allowed to stand for one hour. The methylene chloride layer was filtered and then evaporated to dryness. The residue was taken up in 200 µL of heptane for gas chromatographic analysis. If necessary, this 200 µL was concentrated to 50 µL prior to analysis. A detection limit of 100 ppb was reported. The unpublished EPA-Las Vegas laboratory study was reported by the Midwest Research

Institute as using di-isopropyl ether as an extractant for soil samples.[8]

A method for detecting a triaryl phosphate functional fluid in soil samples and forage after a spill from a Trans Canada Pipelines compressor station was developed by the Ontario Ministry of the Environment.[57] The samples were extracted with chloroform, which was then evaporated to dryness and the dry residue examined by infrared spectroscopy. No attempt was made to quantify the amount of triaryl phosphate present but the spectra enabled qualitative assessment of the functional fluid contamination.

Sediment samples could be treated in a similar manner to soil samples.

3.5.3.4 Tissue and plant sampling: The only extensive work on these media has been carried out on fish tissue. The treatment involves grinding of the sample with an organic solvent.

One study employed petroleum ether which was in turn extracted with acetonitrile.[44] The acetonitrile was flooded with water and re-extracted with petroleum ether. The latter extract was further cleaned by adsorption chromatography on a Florisil column. The column was eluted with successive portions of 6,15 and 50% diethyl ether in petroleum ether. The aryl phosphates were recovered in the 50% eluate and analyzed gas chromatographically.

Another study used 95% methanol as the extractant.[48] After extraction the slurry was filtered and the filtrate concentrated by evaporation. The final solution was treated with alcoholic potassium hydroxide to release phenols which were then treated to form trimethylsilyl derivatives for subsequent gas chromatographic analysis.

Vegetation samples would be treated in a similar manner. Di-isopropyl ether was reported as being used in the EPA-Las Vegas laboratory study.[8]

4. RELATIONSHIPS IN THE ENVIRONMENT

4.1 INTRODUCTION

Comprehensive studies regarding TAP/AAPs in the environment only began appearing in the 1970s. The data are incomplete for an adequate environmental assessment of the compounds. Certain features are apparent however and are dealt with in this chapter.

The routes of entry of TAP/AAPs into the environment are briefly discussed, as are recorded effects resulting from accidental releases. This is followed by sections reviewing published information on TAP/AAP levels found in the atmosphere, aquatic and terrestrial segments of the environment and on levels found in biota.

A discussion follows which deals with the various mechanisms that contribute to the dispersion and degradation of TAP/AAPs in the environment. Data obtained from experiments in the environment or in simulated environmental systems are reviewed. These data, combined with physical and chemical information from general studies of the compounds (presented in Sections 3.3 and 3.4), are used to develop a picture of the environmental behaviour of the phosphate esters.

4.2 ENTRY

There is no documentation of data concerning the release of TAP/AAPs from commercial activities. For this reason, it is not possible to give a quantitative estimate of TAP/AAPs released annually to the environment. All that can be done is to discuss the factors which may lead to environmental release. Basically TAP/AAPs enter the environment in one of two forms: combined in polymers or as liquids.

4.2.1 Plastics

Sixty-two percent of TAP/AAPs are used in plastics and 90% of this amount (or some 725 tonnes) is used as flame retardant plasticizers in PVC.

Plastics' compounding is carried out in closed systems at temperatures of 170 to 200° C. Any sporadic emissions to the work environment would be controlled by hooded vents because of the irritant and health risks from exposure to stabilizers and plasticizers. It has been estimated, in a U.S. study, that little loss would occur from these operations.[8]

Most plastic products are eventually disposed of in waste disposal sites. Except for the slight possibility of leaching by ground water (see Section 4.5.2.1) it is likely that the TAP/AAPs remain immobilized for a considerable time. Plastics eventually degrade by microbial action but these degradation conditions almost undoubtedly degrade the plasticizer. One study reported that thin plastic films buried in a dump in Sweden completely degraded in five years but more substantial plastic parts remained.[61]

Polyvinyl chloride may be degraded by UV light. For these polymers significant absorption is found in the range 290 to 400 nm.[62,63]

Other influencing factors are oxygen (or ozone), humidity, physical wetness and temperature.[8] The remote possibility therefore exists that TAP/AAP plasticizers, which do not absorb light at wavelengths above 290 nm, may be slowly released from products exposed to the elements.

Triaryl/alkyl phosphates degrade at temperatures of the order of 400° C. Disposal of plastics by incineration would, therefore, be unlikely as a significant source of atmospheric release of TAP/APPs.

4.2.2 Liquid Triaryl/alkyl Phosphates

Triaryl/alkyl phosphate functional fluids and oil additives, because of their mobility, have a greater potential for release than do combined plasticizers.

In facilities using TAP/AAP hydraulic fluids it is common to have continuous leakage from hydraulic equipment. Both the equipment and floor are typically covered with a film of these fluids.[8] Control fluids in gas pipeline compressors leak continuously into the pipeline and at times become vented to the environment.[64]

Organophosphates in lubricants and hydraulic fluids are often disposed by direct dumping and by leaking to the environment. A U.S. study estimated that perhaps 75% of the consumption of TAP/AAP lubricant additives and functional fluids are disposed of in these ways.[8] We are, however, aware that one of Canada's major airlines collects its used hydraulic fluid and delivers it for incineration by a commercial disposal company.

4.2.3 Cattle Poisoning

With the exception of episodic accidental exposures of humans (detailed in Chapter 7) the one environmental contamination circumstance for which well documented effects on biota exist has been in cattle. A number of accidental poisonings have occurred, some of which are summarized in Table 4-1. The clinical findings and experimental toxicological investigations arising from these incidents are discussed in the following chapter in Section 5.2.2.1.

4.2.3.1 The Louisiana incident: Nicholson details one incident (of three that occurred in Louisiana in 1973) which affected 42 cattle.[68] The cattle were fed molasses that had been stored in barrels previously containing hydraulic fluid used in a nearby pipeline pump station. The manufacturer of the fluid confirmed that it contained tri-o-cresyl phosphate. Two days after the exposure two animals had died, five were recumbent and 25 were afflicted with varying degrees of posterior weakness. The signs of illness progressed over a period of two weeks to flaccid paralysis of the hindlimbs. These changes were irreversible, several animals died due to ascending paralysis involving respiration, some animals were left as cripples and those unable to walk had to be destroyed.

4.2.3.2 Pipeline spills: The first identified poisoning case occurred in 1967 in Rosedale, British Columbia.[65,66] Eighteen heifers were poisoned by Cellulube 150 (a triaryl phosphate fluid containing TOCP) and died. The oil had escaped from a pipeline pumping station next to pasture in which the cattle grazed. A further two animals were affected in the following year after grazing in the same

TABLE 4-1 Some Recorded Poisoning of Cattle by Aryl Phosphates

Incident/Location	Date	Number Potentially Affected	Number Showing Symptoms	Number of Deaths	Reference
Spill from a gas pipeline compressor station, Rosedale, British Columbia	1967	18	18 +2[a]	18	65, 66
Spill from a gas pipeline compressor station, Hussar, Alberta	1971	33	33	4[b]	65, 67
Molasses accidentally contaminated with triaryl phosphate hydraulic fluid fed to cattle, Louisiana, U. S. A.	1973	42	32	several	68
"Reclaimed oil" rubbed on backs of cattle as treatment for ringworm, Barrie, Ontario	1975	50	50	14	66
Spill from a gas pipeline compressor station, Barrie Ontario	1979	32	7	2 +5 destroyed	57

(a) After the spill was cleaned up, animals were put back into the pasture the following year and two additional animals became affected.

(b) These four animals, critically paralyzed, were sacrificed to permit diagnostic investigation.

pasture which reportedly had been cleaned up.

A second case occurred in 1971 in Hussar, Alberta.[65,67] Thirty-three cattle were poisoned by a hydraulic fluid (Fyrquel 150, previously marketed as IMOL-140) and four of the worst afflicted were sacrificed to enable identification of the nature of the disease. The hydraulic fluid had escaped from a pipeline compressor station into an evaporation pond which overflowed during the spring run-off into a creek used to water the cattle.

A further pipeline pumping station incident occurred in 1979 near Barrie, Ontario.[57] Thirty-two cattle were affected, two died and another five were destroyed. The incident received wide newspaper coverage,[69] which occasioned a meeting called by Trans Canada Pipelines and Stauffer Chemical.[64] At this meeting a number of aspects were clarified.

The material now used in the compressor is Fyrquel GT, a product claimed by the manufacturer to be essentially non-toxic as it is based on tri-(tertiary-butylphenyl/phenyl) phosphate. However, Fyrquel GT had only been used since 1977 and then only to top-up the functional fluid reservoir. The previous fluid (another Fyrquel) had contained TOCP as one of its constituents. Analysis of the fluid remaining in the reservoir showed a 0.1% o-cresol component.[57]

Plants growing in the vicinity of a water drainage path from the pipeline compressor station near Barrie displayed symptoms similar to those of oil toxicity.[57] The stems and leaf petioles had lost their turgidity and the leaves appeared flaccid. The foliage was slightly chlorotic and where it contacted the ground it was blackened and tore away easily. The symptoms, most pronounced close to the compressor station fence, decreased rapidly towards the edge of the eroded drainage area but were observed to some degree along most of the drainage pathway. Forage at all other locations in the field did not display symptoms, nor was there any oily residue apparent on the leaf blades.

4.2.3.3 The Belleville incident: Julian et al reported an incident in which 50 cattle were poisoned by "reclaimed oil".[66] This oil was in fact the residue from an upgrading operation carried out on a triaryl phosphate hydraulic fluid by an oil-reclamation company in Belleville. The residual oil had been consigned to a dump from which it was retrieved, by persons unidentified, and distributed as "used oil" -- subsequent investigations found that the distribution covered a large area, with some samples being traced to northern Ontario.[70]

The oil was used on a farm and was applied to the backs and heads of cattle as treatment for ringworm. Some of the cattle were observed to be licking the oil off themselves and one another.

4.3 RECORDED LEVELS IN AIR, WATER AND THE TERRESTRIAL ENVIRONMENTAL SECTORS

Triaryl/alkyl phosphate levels found in environmental samples are summarized in Table 4-2. Although the picture is by no means complete, the values and their distribution give some idea of the poten-

TABLE 4-2 Levels of Triaryl/alkyl Phosphates in the Environment

STUDY AND LOCATION	AIR (units as shown)	WATER (ppb)	SEDIMENT (ppm)	SOIL (ppm)	REFS
Natural water samples from 13 locations in the United States (1979)		TPP <0.1-7.9 (62/32) NPDP <0.1-20 (55/3) CPDP <0.1-9.5 (55/3)	TPP <0.01-4 (40/13) NPDP <0.01-20 (40/17) CPDP <0.01-4 (40/15)		43
Environmental samples obtained in the vicinity of 10 TAP/AAP manufacturers and users in the United States (1979)	ng/m^3 IPDP <0.001-0.1 (20) CDP 0.02 (1) TCP 0.01-2.0 (3)	IPDP <100-100 (7) TAP <100-5000 (4)	IPDP 0.1-8 (6) TCP 2-5 (2) TAP 3-6 (2)	IPDP 0.1-400 (9) CDP 2 (1) TCP 1-4 (2) TAP 4000 (1)	*
Environmental samples obtained in the vicinity of 2 TAP/AAP manufacturers and users in the United States (1977)	$\mu g/m^3$ TAP <1.7 (12/0)	TAP <10 (18/0)		TAP <0.1 (17/0)	59
Drinking water samples from 6 water treatment plants in Eastern Ontario (1980)		TPP 0.0002-0.0026 (12/12) TCP 0.0003 (12/1) TEHP 0.0003 (12/2)			46
Levels measured in workplace air of a U.S. manufacturer of TAPs (1957)	mg/m^3 TAP 0.27-3.4 (NR)				71
Levels measured in workplace air in a U.S. manufacturer of TPP (1960)	mg/m^3 TPP 0.5-29.6 (78)				72
Levels measured in workplace air of an Ontario user of TAP functional fluid (1977)	$\mu g/m^3$ TAP 5 (2)				55
Soil contaminated with TAP functional fluid after a spill from a gas pipeline compressor station in Ontario (1980)				TAP "trace" to "excessive" contamination (20/17)	57

* Results obtained in an unpublished study by the U.S. EPA-Las Vegas Laboratories, reported by the Midwest Research Institute.[8]

CPDP cumylphenyl diphenyl phosphate: TEHP triethylhexyl phosphate: TAP mixed or unspecified triaryl phosphates

Note: Figures presented as < are the detection limits of the particular study.

Figures in parentheses refer to number of samples taken in a particular study. Where available, the number of samples in which TAPs were detected are shown after the solidus. For example, (63/32) shows that 63 samples were analysed, of which 32 had levels above the detection limit.

(NR) The number of samples were not reported.

tial environmental occurrence of the products. It should be noted that, with the exception of a study of Ontario drinking water,[46] samples were obtained from sites in which TAP/AAPs would have been expected to be found (i. e. , areas in the vicinity of manufacturers and users, waterways downstream from such commercial facilities, and in workplace air).

Levels found in air samples are in general very low. The subnanogram per cubic metre quantities found in the vicinity of manufacturing and user facilities were, for the most part, associated with particulates (EPA-Las Vegas laboratory study, reported in reference 8). Because of the low volatility of the substances, this is not an unexpected result and shows that the main route of atmospheric release is via aerosols. Workplace levels, while still low, are many orders of magnitude higher than those of the general environment. The levels found in workplace air of a triaryl phosphate functional fluid user[55] are themselves considerably lower (by factors of 10^2 to 10^3) than those found in manufacturing plants.[71,72] It should be mentioned that these latter levels were recorded in the late 1950s and it is likely that industrial hygiene practices have considerably improved since then.

Where TAP/AAPs have been found in natural waters, concentrations up to the parts-per-billion are reported. As would be expected, the highest concentrations tended to be found close to outfalls of facilities that either manufacture or used the products. Mayer et al demonstrated that substantial concentration of TAP/AAPs occurred in sediments.[43] The mean water concentrations of all samples tested were

0.12, 0.064 and 0.062 ppb for TPP, NPDP and cumylphenyl diphenyl phosphate (CPDP), respectively, while the corresponding mean sediment concentrations were 1.0, 290 and 170 ppb, respectively. The concentration factor between water and sediment therefore appears to be in excess of 1000.

The detection of triphenyl, tricresyl phosphate and triethylhexyl phosphate (TEHP) in drinking water, albeit at very low levels,[46] may be an indication of the ubiquity of TAP/AAPs in the general environment. It was mentioned that other TAP/AAPs may also be present because of the existence of other, unidentified peaks in the chromatograms. The source of triphenyl phosphate (present in all 12 samples analyzed), tricresyl phosphate and triethylhexyl phosphate was not identified. However, the existence of tributoxyethyl phosphate (a plasticizer commonly used in synthetic rubbers), at concentrations often approaching 100 times those of TPP, was observed and may have been due to leaching from washer and gasket material used in drinking water systems. Indeed, the authors report that stagnant tap water contained higher levels of tributoxyethyl phosphate than those obtained after the tap had been allowed to run for some time.

The highest levels of TAP/AAPs found in soil (400 to 4000 ppm) came from samples collected from the vicinity of two TAP/AAP producers (EPA-Las Vegas laboratory study, reported in reference 8). Trace quantities were also found in samples obtained in the vicinity of a steel-making plant. As would be expected, significant soil contamination was found in the area surrounding a gas pipeline compressor station from which a spill of triaryl phosphate fluid occurred.[57] In this case, however, the actual levels were not measured.

4.4 RECORDED LEVELS IN BIOTA

Similar to the incomplete data on the levels and distribution of TAP/AAPs in air, water and terrestrial sectors, few data are available on levels and distribution in biota. Table 4-3 summarizes what data are available. While the information is sparse, it is worth noting that six of the 11 TAP/AAPs considered in this report have been positively identified; additionally cumylphenyl diphenyl phosphate (CPDP) was also found. All the samples were obtained from sites in which TAP/AAPs would have been expected to be found (i.e., waterways downstream from the TAP manufacturing and using facilities and vegetation samples obtained in the vicinity of such facilities).

The only animals in which TAPs have been identified are fish. Twenty-six different species are represented in the data presented in Table 4-3. All were caught in waters that had measurable TAP/AAP levels. Reference to Table 4-2 shows that the concentrations found in fish tissue were in the high ppb range while the comparable water concentrations were in the low ppb range. This finding indicates a bioconcentration effect which is discussed in Section 4.5.2.2. Commercial triaryl phosphates have been identified, on the basis of the individual TAPs found, as the source of this bioconcentration. Pydraul 50E and 115E,[43,44] Houghto-Safe 1120,[44] and triphenyl phosphate[43,44] have been mentioned.

TABLE 4-3 Reported Levels of Triaryl/alkyl Phosphates in Biota

Study and Location	Fish (ppm)	Vegetation (ppm)	Reference
Fish caught in 8 location in the United States	TPP 0.1-0.6 (82/16) NPDP 0.1-0.9 (55/3) CPDP 0.1 (55/1)		43
Fish caught in 3 locations in the United States	TPP 0.06-0.15 (3) TCP 0.04 (1) TXP 0.08 (1) CDP 0.13-0.41 (3) NPDP 0.16-0.50 (3) TAP 0.1-0.3 (3)		44
Vegetation samples obtained from the vicinity of 10 TAP/AAP manufacturers and users in the U.S.		TCP 1 (4) IPDP 0.1-5 (11)	*
Plant and forage samples obtained in the vicinity of a gas pipeline compressor station in Ontario		TAP: "trace" to "excessive" contamination (12/6)	57

* Results obtained in an unpublished study by the U.S. EPA-Las Vegas laboratory, reported by Midwest Research Institute.[8]

CPDP	cumylphenyl diphenyl phosphate
TAP	mixed or unspecified triaryl phosphates

NOTE: Figures in parentheses refer to the number of samples taken in a particular study. Where available, the number of samples in which TAPs were detected are shown after the solidus. For example, (82/16) shows that 82 samples were analyzed, of which 16 had levels above the detection limit.

The few vegetation samples which showed the presence of TAPs were insufficiently studied to indicate the route by which the contamination occurred. Consequently it is unknown whether absorption occurs through the leaf or root systems or whether the contaminants are merely adhering to the plant. An investigation of contamination of forage after a spill from a pipeline compressor station indicated that some contamination of forage surrounding the station may have occurred prior to the spill.[57] In this case it was suggested that low level contamination occurred continuously, probably from the vent of the TAP fluid storage reservoir. It is likely that this release was as a mist generated by the internal pressure of the lubrication system.

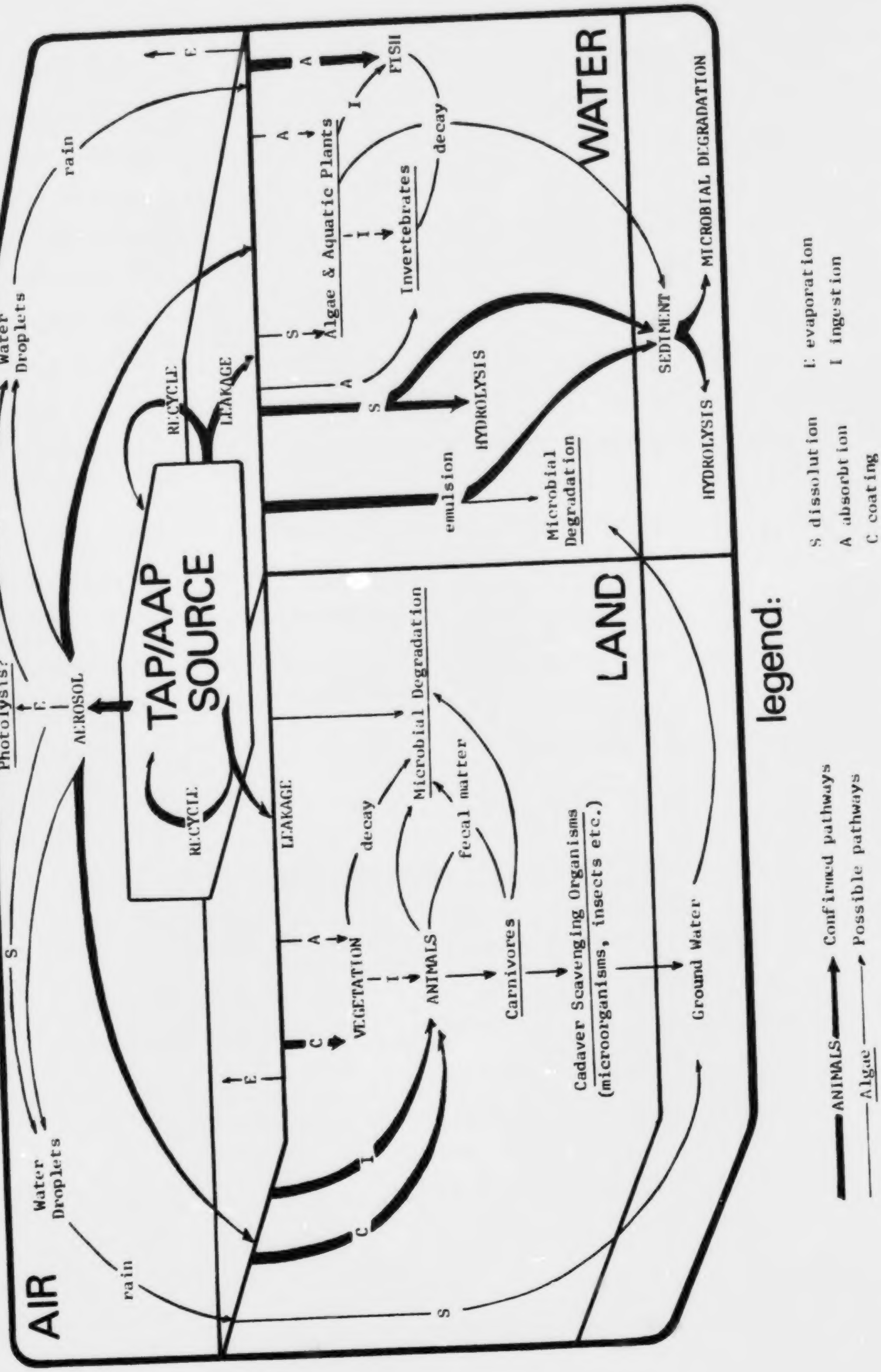
It is clear that very little record exists of levels of TAP/AAPs in biota. Part of this deficiency appears to relate to a previous lack of interest in the compounds since they had been considered environmentally innocuous. A further earlier limitation is suggested by Lombardo and Egry who identify difficulties with specificity in analytical technique.[44]

4.5 TRANSPORT AND ENVIRONMENTAL FATE

With a few exceptions the pathways by which TAP/AAPs are dispersed and degraded in the environment have not been identified. An assessment of transport and environmental fate must therefore be based mainly upon speculative hypotheses, taking into account the physical, chemical and biological mechanisms that would be applicable.

An outline of the possible pathways is given in Figure 4-1.

FIGURE 4-1 Potential Pathways for Transport and Removal of Triaryl/alkyl Phosphates in the Environment



Those routes for which evidence exists are indicated; however, the majority have not been confirmed. Many of the routes may be conjectural, and their acceptance or rejection must await further research. Neither is it possible to make a value judgement on the persistence of TAP/AAPs in the total environment. In most cases the data do not exist, particularly as the pathways through the environment are predominantly speculative.

4.5.1 Air

Triaryl/alkyl phosphates have low vapour pressures. Hence the main route into the atmosphere will likely be through the generation of aerosols. Despite low vapour pressures, however, direct evaporation (from spills or the surface of aerosol particles, for example) and evaporation from water bodies cannot be dismissed as transportation mechanisms. Degradation in the atmosphere has not been studied but photolysis and oxidation are remotely possible.

4.5.1.1 Volatility: The vapour pressures of TAP/AAPs are too low at ambient temperatures to enable direct measurement and recourse to extrapolation methods has to be made. The data on vapour pressures of some commercial TAP/AAPs presented in Table 4-4, were obtained from vapour pressures at elevated temperatures published in manufacturers' technical data sheets. Extrapolation to ambient temperatures (25° C) was made using the Clausius-Clapeyron relationship, which relates saturated vapour pressure of an ideal liquid to the heat of vaporization (ΔH_v) and to temperature.

TABLE 4-4 Vapour Pressures of Some Commercial TAP/AAPs*

Trade Name	Major Component	ΔH_v kJ/mole	v.p. 150° C Pa	v.p. 25° C Pa
Monsanto TPP	TPP	82.8	20.0	9.9×10^{-4}
Santicizer-140	CDP	86.2	10.7	3.6×10^{-4}
Santicizer-154	BPDP	82.8	14.7	7.2×10^{-4}
Santicizer-141	EHDP	67.4	27	8.4×10^{-3}
Santicizer-148	IDDP	52.3	13	2.5×10^{-2}

* Calculated from data presented in trade literature using the Clausius-Clapeyron relationship:

$$\ln (\text{v.p.}) = -\Delta H_v/RT + C$$

where v.p. is the vapour pressure at temperature T (°K), ΔH_v is the heat of vaporization of the liquid, R is the universal gas constant and C is a constant of integration. Only those products for which there were at least three vapour pressure values at different temperatures, and which produced a linear plot of ln (v.p.) vs 1/T are included in the table.

Although the products listed in Table 4-4 are probably mixtures of TAPs or AAPs it is possible to identify some general features The triaryl phosphates have similar heats of vaporization and have the lowest vapour pressures. The tri-(alkyl aryl) phosphates have lower heats of vaporization and, consequently, higher (although still very low) vapour pressures.

The possibility of direct volatilization is demonstrated by the results of a study carried out by the U. S. Environmental Protection Agency (EPA-Las Vegas laboratory study, reported in reference 8). This study involved taking samples from automobile windows. The interior sides of the windows of two cars were rubbed with glass wool swabs to determine if TAP plasticizers were being evaporated and condensed on the relatively cool window surface. The swabs were extracted with isopropyl ether and the extract, after concentration, was injected into a gas chromatograph. Tricresyl phosphate was identified in swabs from both cars.

Contaminants with low water solubilities may be capable of evaporation from water bodies even though they also have low vapour pressures. Mackay and Wolkoff derived a relationship to predict the evaporative half-lives of such compounds from continually mixed water bodies.[73] The evaporative half-lives of some TAP/AAPs calculated, for water of one metre in depth, using this relationship are presented in Table 4-5. It may be seen that, with the possible exception of tri (alkyl/aryl) phosphates (namely EHDP and IDDP) evaporation from water bodies is unlikely to be an environmentally significant transport mechanism for TAP/AAPs.

TABLE 4-5 Calculated Evaporative Half-lives (at 25° C) of Some Triaryl/alkyl Phosphates[(a)]

Compound	Solubility[(b)] mg/L	Vapour Pressure[(c)] Pa	Half-life Days
TPP	1.9	9.9×10^{-4}	85
CDP	2.6	3.6×10^{-4}	306
BPDP	3.2	7.2×10^{-4}	168
EHDP	1.9	8.4×10^{-3}	9
IDDP	0.75	2.5×10^{-2}	1

---

a) Evaporative half-lives ($t_{1/2}$) were calculated from a relationship developed by Mackay and Wolkoff[73] to predict evaporation rates, from continually mixed water, of negligibly soluble compounds with low vapour pressures:

$$t_{1/2} = \ln(2)\, G\, M_w P_w C_{is} \;/\; (E P_{is} M_i)\; 10^6$$

where G is the amount of water in the sample (1×10^6 g for water 1 m deep and with a surface area of 1 m^2) and E is the rate of evaporation of water from the sample (assumed by Mackay and Wolkoff to be 2740 g/day for typical N. American water bodies); M_w and M_i are the molecular weights of water and the contaminant, respectively; P_w and P_{is} are the vapour pressures of water and the contaminant, respectively; and C_{is} is the water solubility of the contaminant.

b) From solubilities of commercial single compounds reported by Saeger *et al.*[74]

c) Vapour pressures of commercial TAP/AAPs presented in Table 4-4.

4. 5. 1. 2 Photolysis: Ultraviolet photolysis of triaryl phosphates produces biaryls and monoaryl phosphates as major reaction products.[35] Whether such a reaction is possible under atmospheric conditions is questionable because TAP/AAPs show little to no absorption at wave lengths above 290 nm "cut-off" of sunlight (see Section 3. 4. 3. 2).

4. 5. 1. 3 Oxidation: Triaryl/alkyl phosphates are unlikely to oxidize in the atmosphere. The very fact that they are used as fire retardants demonstrates their resistance to oxidization. They may, however, be attacked by reactive atmospheric species, such as nitrogen oxides. If this were the case, reaction would probably occur at the aryl groups by substitution. There are, however, no studies which demonstrate the feasibility of such reactions with TAP/AAPs.

4. 5. 2 Water

Despite their low solubility, water is the major dispersive and degradative medium of TAP/AAPs in the environment. The phosphate esters are transported mainly as suspensions from which, in view of their predicted potential to preferentially concentrate in soils, they may concentrate in sediments. Hydolysis, which is apparently accelerated by microbial action, is the major degradation mechanism. High octanol/water partition coefficients indicate the potential for bioconcentration in aquatic organisms.

4. 5. 2. 1 Solubility characteristics: Water solubilities and octanol/water partition coefficients are available for most of the TAP/AAPs considered in this report. Table 4-6 summarizes the

TABLE 4-6 Water Solubilities, Octanol/Water Partition Coefficients and Estimated Bioconcentration Factors

Compound*	Water Solubility ppm	Octanol/Water Partition Coefficients	Estimated Bioconcentration Factor	Reference
TPP	1.9	4.2×10^4	420	43,74
TCP	0.36	1.3×10^5	750	74
TXP	0.89	4.3×10^5	1400	74
CDP	2.6	3.2×10^4	360	74
IPDP	2.2	2.0×10^5	970	74
BPDP	3.2	1.3×10^5	770	74
NPDP	0.77	8.6×10^5	2100	43
CPDP	0.063	1.2×10^6	2500	43
DBPP	96	1.9×10^4	270	74
EHDP	1.9	5.3×10^5	1600	74
IDDP	0.75	2.7×10^5	1100	74

Note: CPDP refers to cumylphenyl diphenyl

* All compounds listed are commercial grade materials.

available data.

The water solubilities are low and exhibit a wide range of values among the individual compounds. There does not, however, appear to be any easily discernible relationship between the structure of TAP/AAPs and their water solubilities.

Despite their low solubility, TAP plasticizers may become leached from the plastic. Data illustrating the leaching potential of some TAP/AAP plasticizers are available from manufacturers' data sheets and are presented in Table 4-7. The data were obtained from weight loss tests in which PVC, containing 50 parts of plasticizer to 100 parts of PVC resin, was immersed in water for 24 hours. The small weight loss, of the order of fractions of a percent, indicate that the plasticizer can be removed by water action. Tri-(alkyl aryl) phosphate plasticizers exhibit a marginally higher leachability than triaryl phosphates. Ahrens et al indicated that samples of vinyl upholstery fabric commonly employed in automobile interiors can release TPP when placed in water and the resulting solution is toxic to goldfish.[76]

4.5.2.2 Bioconcentration: Octanol/water partition coefficients for TAP/AAPs are high and have been used to estimate the potential for bioconcentration in fish. The values for bioconcentration factors presented in Table 4-6 were calculated by Mayer et al[43] and Saeger et al[74] from a relationship derived by Neely et al[75] for rainbow trout:

$$\log (\text{bioconcentration factor}) = 0.542 \log (\text{partition coefficient}) + 0.124$$

TABLE 4-7 Leaching Potential of PVC Containing Triaryl/alkyl Phosphate Plasticizers*

Plasticizer	Trade Name	% Weight Loss After Immersion in Water For 24 Hours
TCP	-	0.06
CDP	-	0.10
IPDP	-	0.06
BPDP	Santicizer 154	0.04
EHDP	Santicizer 141	0.25
IDDP	Santicizer 148	0.16

Source: Monsanto Industrial Chemicals Co., technical data sheets.

The detection of TAP/AAPs in tissue samples of fish caught in natural waters contaminated by TAP/AAPs is complemented by laboratory studies carried out on trout.[43,44] The fish were exposed to several concentrations, in the ppb range, of TAP/AAPs for 90 days. After this time period, the fish were sacrificed and the levels of TAP/AAPs in their tissue measured. The results obtained are shown in Table 4-8.

The experimentally measured bioconcentration factors were similar to those estimated from octanol/water partition coefficients for TPP, NDPD and CPDP. Although the experimentally determined factors for NPDP were lower than expected, the overall agreement was considered generally supportive of the relationship used by the authors to derive the expected bioconcentration factors from octanol/water coefficients.[43]

The average depuration half-life for TPP, NPDP and CPDP have been reported by Mayer et al as 0.54, 3.4 and 5.9 days, respectively.[43] These values were obtained from rainbow trout exposed to the compounds in a flow-through system for 90 days, after which time dosing was terminated and fish were sacrificed periodically and the residual TAP/AAP concentrations in their tissue were measured.

The data obtained from environmental samples (Table 4-2) together with the experimental bioconcentration studies show that fish accumulate TAP/AAP compounds in contaminated environmental settings and may, therefore, be a species at risk. To what degree

TABLE 4-8 Experimentally Determined Bioconcentration Factors in Trout

Triaryl Phosphate	Bioconcentration Factors[(a)]	
	Experimental	Calculated
Pydraul 50E		
TPP	314 (217)	
NPDP	444 (133)	
CPDP	2218 (1157)	
Pydraul 115E		
TPP	-	
NPDP	271	
CPDP	760	
Single Compounds		
TPP	271	420
NPDP	691	2100
CPDP	2807	2500

(a) These values were obtained by Mayer et al[43] except the figures in parentheses which were obtained by Lombardo and Egry[44] for Pydraul 50E.

the contamination comes significantly and directly from water is unknown. Accumulation and transfer by way of food chain components is also possible.

4.5.2.3 Hydrolysis: The chemical properties of TAP/AAPs, presented in Chapter 3, indicate that phosphate triesters will be comparatively rapidly hydrolyzed to the corresponding diesters, particularly under alkaline conditions. Two recent studies have shown that this is indeed the case.[74,77]

The half-lives for the hydrolysis of TPP, NPDP and CPDP at various pH levels in buffered solutions at ambient temperatures are presented in Table 4-9. These half-lives were obtained by measuring the disappearance of the triaryl phosphate. The effect of pH is clearly evident. In addition, NPDP and CPDP appear to be more slowly hydrolyzed than TPP.

The effect of pH may be more clearly seen from Figure 4-2 which shows for TPP an approximately linear relationship between the logarithm of hydrolysis half-life (log $t_{1/2}$) and pH. This graph may be used to gain some idea of the range of half-lives to be expected at environmental pH levels: varying from approximately 1 day at pH 10 to about 365 days at pH 4. It should be noted, however, that as pH decreases the importance of H_2O as a nucleophile relative to the hydroxyl ion will increase and the upper limit for $t_{1/2}$ may be lower than indicated.

In natural waters pH is only one factor contributing to hydrolytic degradation of TAP/AAPs. The presence of sediment and aquatic

TABLE 4-9 Hydrolysis Half-Lives (in days) for TPP, NPDP and CPDP at Various pH Values

Compound	9.5	9.0	8.2	7	5	Reference
TPP	1.3		7.5			77
TPP		3		19	>28	43
NPDP		6		>28	>28	43
CPDP		5		>28	>28	43

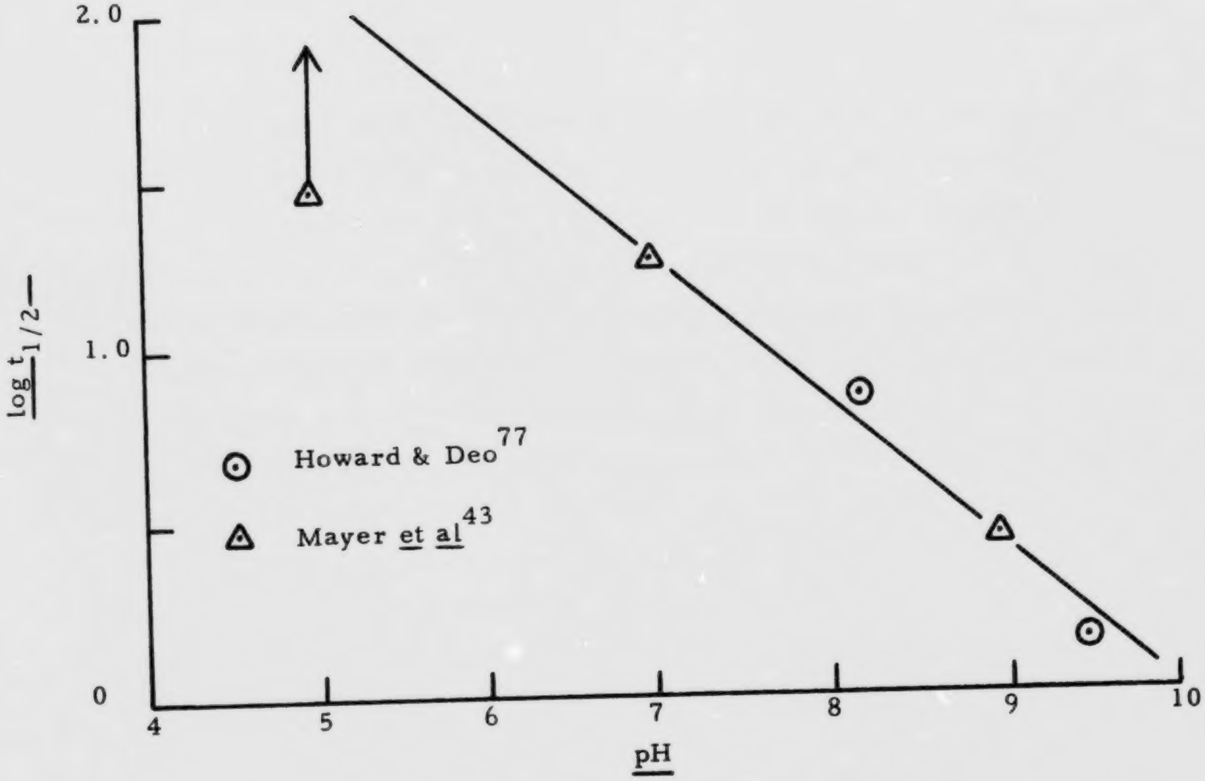


FIGURE 4-2 Relationship Between Hydrolysis Half-Life and pH for TPP (data from Table 4-9)

micro-organisms have been shown to markedly increase hydrolysis rates. Howard and Deo compared the disappearance of TPP in Lake Ontario water and Seneca River water (both at an initial pH of 8.2) with that obtained in buffered demineralized water (also at pH 8.2).[77] They found half-lives of 1.1, 2.0 and 7.5 days for Lake Ontario water, Seneca River water and demineralized water, respectively. Mayer *et al*, in a microcosm study under simulated lake water conditions, demonstrated the importance of both sediment adsorption and degradation as mechanisms for removal of TAPs from water.[43] The data are shown in Table 4-10. After 28 days less than 10 µg/L of each compound remained in non-sterile water samples following an initial dosing of 1 mg/L Pydraul 50E (which contains TPP, NPDP and CPDP). The NPDP and CPDP components rapidly disappeared from non-sterile water samples (90% in less than 3 days); disappearance of TPP was somewhat slower (50% in approximately 3 days). This slower rate was attributed to the greater water solubility of TPP, compared with NPDP or CPDP (see Table 4-6). The purge gas (air versus nitrogen) or level of light did not appear to have a significant effect on the disappearance rates.

Saeger *et al* produced data which demonstrate a structural effect on TAP disappearance rates in river water.[74] In this study, disappearance curves for eight TAP/AAPs were presented. The data were obtained in three separate experiments, using river water samples obtained from the same source at different times, but in each case the curve for the disappearance of TPP was presented.

Approximate values for the time taken for 50% of the TAP/AAP to disappear may be obtained by inspection of these curves. In each

TABLE 4-10 Disappearance of TPP, NPDP and CPDP in Microcosms Simulating Lake Conditions[43]

Microcosm Core Conditions	Time to 90% Disappearance (Days)		
	TPP	NPDP	CPDP
Non-sterile, aerated, light	14	<3	<3
Non-sterile, aerated, dark	10	<3	<3
Non-sterile, nitrogen purge, light	10	7	7
Sterile, aerated, light	>28	21	21
Sterile, nitrogen purge, light	>28	>28	>28

of the experiments an approximate idea of the hydrolytic stability of each TAP/AAP relative to that of TPP may be obtained by dividing the time taken for 50% disappearance of each TAP/AAP by that taken for TPP. If it is assumed that the composition (i. e., pH, sediment concentration, microbial population, and so on) of the three river water samples were approximately the same in each experiment, the hydrolytic activities of each TAP/AAP may be compared. The comparisons are presented in Table 4-11 and show the following approximate hydrolytic activity series:

$$\mathrm{TPP} \cong \mathrm{CDP} \cong \mathrm{TCP} > \mathrm{DBPP} \cong \mathrm{EHDP} \cong \mathrm{BPDP} > \mathrm{IPDP} > \mathrm{IDDP}.$$

In another experiment, which also demonstrates an effect of structure on hydrolysis, Howard and Deo determined rates of disappearance of three isomers of TCP (tri-o-cresyl, tri-m-cresyl and tri-p-cresyl phosphates) in Lake Ontario water and found that the ortho-isomer degraded slightly faster than the meta-isomer and both isomers degraded faster than the para-isomer.[77]

An earlier study produced markedly different results, to those from the studies discussed above, for the hydrolytic degradation of a commercial triaryl phosphate (IMOL-140) in both demineralized water and in river water.[65] The authors reported apparent degradative half-lives of 73 and 96 days for IMOL-140 in demineralized water and river water respectively. Also, in contrast to the results of Mayer *et al*,[43] they found that light (both fluorescent and sunlight) markedly increased the apparent disappearance rate. But the researchers estimated the disappearance of IMOL-140 by measurement of the production of the ultimate degradation product, orthophosphate. Given that the rate

TABLE 4-11 Relative Hydrolytic Activities of a Number of TAP/AAPs in River Water*

Compound	Time Taken for 50% Disappearance Divided by the Time Taken for Triphenyl Phosphate
TPP	1.0
TCP	1.3
CDP	1.2
IPDP	2.6
BPDP	1.8
DBPP	1.6
EHDP	1.7
IDDP	5.5

* Derived from data presented by Saeger et al.[74]

The TAP/AAPs were commercial grade compounds.

of hydrolysis of diesters is very much slower than the rates for either the corresponding triesters or monoesters (Section 3. 4. 3. 3), it is probable that the experiments measured mainly the fate of phosphate diesters.

4. 5. 2. 4 Microbial degradation: The fact that disappearance is more rapid in natural waters than in sterilized natural waters or in demineralized water at the same pH, indicates that biodegradation is probably an important factor in the disappearance of TAP/AAPs from aquatic environments.

Saeger et al made an extensive study of the fate of a number of TAP/AAPs in activated sewage.[74] They showed that TPP, TCP, CDP, BPDP, EHDP and DBPP degraded rapidly, while TXP, IPDP and IDDP degraded somewhat more slowly. Studies into the ultimate biodegradability were carried out by measuring the evolution of carbon dioxide produced in the sewage digestion. The carbon dioxide yield, when compared to the theoretical amount possible from the carbon content of the ester, was indicative of the rate of digestion. The same rate trends were observed in the CO_2 evolution studies as were observed in the activated sludge tests and the authors concluded that the esters broke down completely to carbon dioxide, water and inorganic phosphate.

They suggested that the degradation pathway for the esters most likely involves a stepwise enzymatic hydrolysis to orthophosphate and the phenolic or alcoholic moieties. These moieties would then be expected to undergo further degradation. From an overall viewpoint, it was concluded that for alkyl aryl phosphates, the shorter the alkyl chain the more biodegradable the ester. For tri-(alkyl aryl) and triaryl esters, increasing the number and size of substituent groups leads to decreasing biodegradability. The authors found no obvious correlation between solubility and biodegradation.

4.5.3 Terrestrial Environment

Mayer et al[43] calculated soil sorption coefficients (soil/water partition coefficients) for TPP, NPDP and CPDP from their water solubilities and octanol/water partition coefficients using a method developed by Kenaga and Goring:[81] values of 5.5×10^3, 2.3×10^4 and 3.4×10^4, respectively were determined. These relatively high values indicate the potential for preferential concentration of TAP/AAPs in soil and sediments. Indeed, the authors concluded that the low water solubilities and high soil sorption coefficients suggested that sediments control TAP/AAP concentrations in the aquatic sector.

The major portion of TAP/AAPs consumed in Canada (62%) are used as flame retardant plasticizers and may eventually be disposed of in landfill sites as solid plastic waste. In addition, TAP/AAP functional fluids may enter the environment either as aerosols or from accidental spills. In each case soil may become contaminated with the compounds. The high soil sorption coefficients indicate that soil may therefore be the major environmental sink of TAP/AAPs.

There have been few investigations into the fate of TAP/AAPs in terrestrial samples. Pickard et al used a microbial culture from a mud sample obtained from the bottom of a lake in the Northwest

Territories to determine whether microbial action was capable of degrading triaryl phosphate esters.[78] The mixed microbial population was found to be able to use Fyrquel 220, TOCP, TXP and, to a limited extent, TPP as the sole carbon source for growth. The soil sample from which the culture was extracted was obtained from a lake which had been subjected to extensive contamination with aeroengine fuels and other oils, and was an excellent source of oil-utilizing microorganisms. The authors concluded, however, that while many soils undoubtedly contain TAP degrading microbes, it was questionable whether all soils can be expected to contain an indigenous microbial population capable of using oils as a sole carbon source.

Although there are indications that some thermophilic fungi can utilise TAPs as an energy source under laboratory conditions,[79] triaryl phosphates incorporated as plasticizers in PVC may not be readily degraded by microbial action under conditions in waste disposal sites. In one experiment, weighed samples of PVC (containing 100 parts polymer, 50 parts plasticizer, 2 parts stabilizer and 0.5 parts lubricant) were placed between soil layers (at pH 6.9) and inoculated with Pseudomonas and Brevibacterium species.[80] After eight weeks burial at a soil humidity of 30% and a temperature of 22 to 25° C the samples were retrieved, dried and weighed and any weight loss together with degradation of physical characteristics was interpreted as an indication of microbial action. It was found that degradation was largely dependent on the nature of the plasticizers, with no evidence for any attack on the polymer itself. None of the samples (each of which contained a different plasticizer) showed much degradation over the experimental time period and phthalate and phosphate (TXP, TCP) esters showed the greatest resistance. In fact the sample containing TCP plasticizer showed only a 0.1% weight loss while that containing TXP showed no detectable weight loss.

4.6 SUMMARY

The available data indicate that TAP/AAPs are found in all three sectors of the environment: namely, air, land and water. In addition, uptake by biota has been recorded in a few instances: specifically in cattle, fish and vegetation. Information is far from complete and definitive statements on the persistence and degradation of TAP/AAPs in the envrionment cannot be made. The major features are summarized in Table 4-12.

The majority of studies on the environmental effects of TAP/AAPs deal with the aquatic environment and it appears likely that water is both the major medium for dispersion of TAP/AAPs and the main agent for degradation in the environment -- particularly through microbial degradation. Soil and aquatic sediments appear to be the major sites for potential accumulation of the compounds.

The question of persistence of TAP/AAPs basically depends on their reactivities in the various environmental sectors. Since solubilities are low, the rate of transfer from a liquid residue or from a sediment sink is likely to be slow in a static situation. On the other hand, if conditions were such that TAP/AAPs were able to dissolve more readily, such as in a dynamic water system, total disappearance could occur within a couple of weeks. (The 1300 tonnes of TAP/AAPs imported into Canada annually would only require some

TABLE 4-12 Summary of General Properties of TAP/AAPs and the Mode of their Interaction in the Environment

TAP/APP Property	Mode of Interaction in the Three Environments		
	Atmospheric	Aquatic	Terrestrial
Vapour pressure	Low volatility (~10^{-3} Pa); limited data on transport; probably via aerosols.	Due to low solubility and low vapour pressure, evaporation not a significant transfer pathway; evaporation from water?	Insignificant exchange from soil to atmosphere due to low vapour pressure and high soil sorption potential; co-evaporation with water?
Solubility	N/A	Low solubility, probably carried into aquatic environments by physical suspension; potential concentration in aquatic sediments. Wide range of solubilities among individual TAP/AAPs.	Limited leachability from soil presumed; also limited leaching from disposed plastics possible.
Hydrolysis	N/A	The major degradative route, enhanced by microbial action and alkaline waters; evidence of structural effects on hydrolysis rates.	Hydrolysis possible, but not identified; microbial action possible.
Persistence	No data available but likely to be short.	Degradative half-life in natural waters may range from 1 to 7 days, if sediment and micro-organisms present and the TAP/APPs are in solution.	Unknown; high soil sorption coefficients; degradation would depend on soil alkalinity, moisture content, microbial population.
Bioaccumulation	No data available on birds or insects.	Bioaccumulation noted and confirmed in fish.	No available data on higher forms of animal life.

N/A - not applicable

10^9 m^3 of water to dissolve them -- the volume of a medium sized lake such as Lake Simcoe in Ontario!) It should, however, be remembered that phosphate triesters hydrolyse to the corresponding diesters which, in addition to being moderately soluble in water (to about 3%), have much slower rates of hydrolysis. No data on the toxicities or the existence in the environment of such diesters were found, so their potential impact is unknown.

5. EXPERIMENTAL TOXICOLOGY

5.1 INTRODUCTION

This section will deal with experimental assessment of the dynamics of TAP/AAP exposure as well as their toxicity effects. These experimental studies may be separated for convenience and practicality into examinations of species of environmental or economic significance and studies of those species normally considered in laboratory bioassays of toxicity. These sections will be referred to as environmental and pharmaco-toxicology, respectively. In the first instance, the experimental studies, whether carried out in the field or laboratory environment, will relate to contaminant levels and effects resulting from incidental exposures as referenced in Chapter 4 of this report. Toxicological experimentation on recognized laboratory test species, such as mouse, rat, and guinea pig, among others, has more relevance to the human condition, insofar as these species have an exceptionally well documented comparative biology. (Occasional human experimentation may also be included here.) Their responses to a wide variety of toxicants have formed a baseline of toxicity assessment, standardized against the recorded or anticipated human response. These assessments also frequently form the basis of contaminant regulations in environmental health.

Experimental studies are necessary to allow definition of toxic responses. The virtual impossibility of controlling or even accounting for all the relevant variables found in an environmental setting prevents effective characterization of contaminant toxicity. Experimental animal studies, with their more rigorous control of such variables as age, sex, season, diet and others, will form a basis of knowledge which will have predictive properties. It is unfortunate that, in the case of the TAP/AAP compounds, the experimental information is disparate. This results mainly from the small amount of experimental work which has been carried out, particularly on environmentally significant species. The diversity of chemical compounds represented by the TAP/AAPs under study (see Chapter 3) is a further major confounding factor. This diversity results perhaps less from differences in their chemical nature, than from their biological reactivity expressed by toxicity effects.

5.2 ENVIRONMENTAL TOXICOLOGY

5.2.1 Uptake, Distribution and Clearance

A comparative assessment of the uptake routes of TAP/AAPs is limited to empirical interpretations based on the particular conditions of the exposure regime. A number of studies in fish, for instance, **have** shown toxic effects following exposure to water soluble fractions of TAP/AAPs (see Table 5-2). The route of entry in these cases may be assumed to be primarily by way of the gill surface, although skin absorption is a further possibility. Daphnids and midges were susceptible to Pydraul 50E in water.[43] Surface absorption is also suggested in studies on the potentiation of organophosphate insecticides by TAP/AAPs in insects.[87-90] A ready transfer across the insect cuticle is suggested.

Oral dosing as a vector of exposure was also effective in the production of toxicity responses in insects.[91] In fish as well, gut uptake can be considered as a route of entry, as shown by an ongoing study on the effects of TPP, carried out at the Canadian Centre for Inland Waters, Burlington, Ontario.[92] The gastrointestinal route has received particular attention in studies of livestock species. Cattle treated experimentally with Fyrquel ^{TM} 150 by oral dosing showed similar toxicity symptoms as cattle exposed accidentally in pasture.[93] Other economic domestic species also showed toxicity signs when TAP was administered orally.[94]

It is not possible to estimate the hazard to the animal of TAP/AAPs as related to the route of entry of the compounds. Both oral, gill surface, and cutaneous exposures have been identified as resulting in toxicity.

The dynamics of uptake, distribution and clearance of the organophosphates under discussion have been defined to date only in fish. A study by Lockhart *et al* identified an accumulation of IMOL S-140 compounds, assessed as cresols derived from IMOL S-140 hydrolysis, in rainbow trout tissues.[83] Four months of exposure to a water concentration of 900 µg/L IMOL S-140 in a flow-through system resulted in an accumulation in white muscle and, particularly, in digestive tract tissues, including accessory and adipose tissues (Table 5-1). A comprehensive study by Mayer *et al* on an aquatic environmental assessment of Pydraul 50E and 115E using rainbow trout fry as one of the target organisms showed dose-dependent accumulation of three of the components of the two hydraulic fluids.[43] The compounds TPP, NPDP and CPDP were measured. No residue

TABLE 5-1 Accumulation of Triaryl/alkyl Phosphate Compounds in Rainbow Trout (Salmo gairdneri) Tissues

Compound	Exposure Concentration µg/L	Duration of Exposure	Tissue Level (µg/g) White Muscle	Tissue Level (µg/g) Cut Tissue	Tissue Level (µg/g) Whole Fish (Fry)	Reference
IMOL S-140	900	4 mos.	9	152		83
Pydraul 50E	1 to 15	90 days				43
TPP					0. 13 to 1. 0	
NPDP					ND to 1. 3	
CPDP					0. 32 to 3. 0	
Pydraul 115E	58 to 34	90 days				43
TPP					ND	
NPDP					0. 15 to 1. 6	
CPDP					0. 81 to 14	
TPP	0. 22 to 1. 4	90 days			0. 08 to 0. 41	43
NPDP	0. 36 to 4. 2	90 days			0. 33 to 1. 3	43
CPDP	0. 22 to 2. 0	90 days			0. 55 to 3. 3	43

storage interactions were detected and the tissue concentrations of the three TAPs were similar whether the fish were exposed to the individual compounds or to their presence in the hydraulic oils at comparable absolute levels. Mayer et al calculated a bioaccumulation in rainbow trout fry, after 90 days of exposure of 271, 691 and 2,807 times the levels of TPP, NPDP and CPDP, respectively (see Section 4.5.2.2). Sitthichaikasem determined depuration half-lives for these compounds in rainbow trout, as 0.54 days for TPP, 3.4 days for NPDP, and 5.9 days for CPDP.[85] There is good correlation between the greater bioaccumulation of CPDP, for instance, and its longer biological half-life.

5.2.2 Toxic Effects

5.2.2.1 Acute toxicity: The bulk of comparative information on toxic effects exists for fish species, not only for the acute exposures discussed here but also for chronic exposures described below. The acute exposure regimes are generally of high contaminant concentration and for a short duration only, up to about 30 days of exposure.

Values for LC_{50} levels of contamination have been calculated for a large number of fish species, and are given in Table 5-2. This includes 24-hour and 96-hour LC_{50} calculations for a wide variety of TAP/AAPs. Of the formulated compounds, it appears that Pydraul 115E has the least acute toxic effect in all species of fish examined, both with regard to LC_{50} calculations as well as to other signs of toxicity. The fluid IMOL S-140, as examined in rainbow trout, had less of an acute toxicity than either Houghto-Safe 1120 or Pydraul 50E.

TABLE 5-2 The Toxic Effects of Acute Exposure to Triaryl/alkyl Phosphates in Aquatic Organisms

Species	Test System	Compound	LC_{50} (mg/L)		Clinical Signs	Reference
			24 Hr	96 Hr		
Algae (*Selenastrum capricornutum*)	static	Pydraul 50E		5		43
		Pydraul 115E		>1000		
		TPP		2		
		NPDP		>1000		
		CPDP		>1000		
Daphnid (*Daphnia magna*)	static	Pydraul 50E		7.8 (48 hr)		43
		Pydraul 115E		13		
		TPP		1.0		
		NPDP		96		
		CPDP		>560		
Mysid shrimp (*Mysidopsis bania*)	static	Pydraul 50E		0.27		43
		Pydraul 115E		0.70		
		TPP		>0.18 <0.32		
		NPDP		20		
		CPDP		9.4		
Midge larvae (*Chironomous plumosus*)	static	Pydraul 50E		1.6 (48 hr)		43
Guppy (*Poecillia reticulata*)	static	IMOL S-140	>14		none	65
Rainbow trout (*Salmo gairdneri*)	static	IMOL S-140	>14		none	65
	static	Houghto-Safe 1120	4.2	1.7	none or few	84
		Pydraul 50E	1.3	0.72		
		Pydraul 115E	>100	45		
	flow-through	Houghto-Safe 1120		0.65	none or few	
		Pydraul 50E		0.67		
	static	Pydraul 50E		2.0		43
		Pydraul 115E		10		
		TPP		0.4		
		NPDP		>100		
		CPDP		>100		

TABLE 5-2 (cont'd.)

Species	System	Compound	LC_{50} (mg/L)		Clinical Signs	Reference
			24 Hr	96 Hr		
fry	static	Pydraul 50E	3.4	1.7	hemorrhagic areas beneath dorsal fins at high doses	85
		TPP	>0.56	0.31		
fingerling		Pydraul 50E	2.0	1.3		
		TPP	0.62	0.32		
Fathead minnow (*Pimephales promelas*)	static	Houghto-Safe 1120	>90	35	anorexia, hypersensitivity, hemorrhages at base of dorsal fins	84
		Pydraul 50E	2.5	1.3		
	flow-through	Houghto-Safe 1120	17			
		Pydraul 50E	2.1			
	static	TPP	0.66			43
		NPDP	>1000			
		CPDP	>1000			
Sheepshead minnow (*Cyprinodon variegatus*)	static	Pydraul 50E	1.9			43
		Pydraul 115E	7.1			
		TPP	>0.32 <0.56			
Channel catfish (*Ictalurus punctatus*)	static	Houghto-Safe 1120	130	43	anorexia, hypersensitivity, hemorrhages at base of dorsal fins	84
		Pydraul 50E	7.2	3.0		
		Pydraul 115E	>100	>100		
	flow-through	Houghto-Safe 1120		>15		
		Pydraul 50E		2.4		
Bluegill (*Lepomis machronchirus*)	static	Houghto-Safe 1120	32	12	marked anorexia, hypersensitivity, abnormal swimming pattern, hemorrhage at base of dorsal fins	84
		Pydraul 50E	4.4	2.2		
		Pydraul 115E	>100	>100		
	flow-through	Houghto-Safe 1120		11		
		Pydraul 50E		2.8		
	static	IDDP		6.7		82
		TCP		7.0		
		TPP		0.29		
	static	Pydraul 50E	3.2	2.7	hemorrhages at base of dorsal fins	85
		TPCP	>100	>100		
Tidewater Silversides (*Menidia beryllina*)	static	IDDP		1.4		82
		TCP		8.7		
		TPP		0.10		

Considering the individual organophosphates, the order of decreasing acute toxicity was TPP, IDDP, TCP, and, as a group, CDP, NPDP and CPDP. This order is irrespective of species. Of the individual species, rainbow trout appear to be the most sensitive as far as lethality is concerned, but less so with regard to other and clinical acute toxicity signs. In the latter respect, bluegills are the most sensitive of the fish species examined. An age comparison is possible for rainbow trout. An evaluation of all the experiments which have been carried out suggests similar susceptibility of trout fry and fingerling and larger fish to Pydraul 50E and TPP. A comparison of static versus flow-through test systems suggests slightly greater toxicities in flow-through systems, in that LC_{50} values were greater, in most cases, in the latter. A ready explanation is lacking, but such a difference may be perhaps attributed to breakdown of the TAP/AAPs, with a greater proportion of conversion products present in static systems. The relative toxicities of breakdown products have not been established.

Acute toxicity responses have been examined in other aquatic organisms (Table 5-2). Algae, daphnids, and mysid shrimp show generally the same order of responsiveness to formulated and individual TAP/AAPs as has been described for fish species.

The clinical and pathological effects observed in cattle after accidental contamination by TAP/AAPs (see Section 4. 3. 2) are well described by Julian _et al_,[66] Beck _et al_,[67] Nicholson,[68] and Flatla.[95] A common early symptom associated with the apparent ingestion of triaryl phosphate-containing hydraulic fluid was diarrhea followed by a progressive series of delayed toxicity effects.

Within what may be estimated to be a few days to two weeks after exposure, signs of posterior weakness were noted, with knuckling at the the fetlocks and mild ataxia. Some incoordination was observed and the cattle may have had difficulty in rising. Sensation in the hindquarters appeared unaffected. Within a few days, the cattle showed difficulty in standing, with a buckling of the hind legs and incoordination suggestive of loss of proprioceptive coordination when moving. Hindquarter involvement progressed to complete paralysis which was irreversible in many cases. Muscle wasting was evident. In severe cases, the front quarters also showed evidence of motor involvement. Dyspnea was evident with physical activity. Milk production ceased in some cases. A large number of the poisoning cases terminated with the death of the cattle as a direct result of the intoxication (see Section 4. 2. 3). In many other cases, the animals were killed.

Pathology revealed no specific lesions, although a mild bronchopneumonia was recorded in a number of cases. In a few cases, the small intestine seemed to be involved. Histopathological examinations revealed swollen axons undergoing a Wallerian degeneration. Myelin degeneration was significantly preceded by axon death. Degeneration of axons and demyelination occurred particularly in the upper cervical regions of the spinal cord. In the lower cervical regions, as well as thoracic and lumbar regions, the lesions were progressively fewer and more randomly distributed towards the periphery of the cord. Occasional degenerating neurons were found in the brain, and some peripheral degeneration was noted as well, particularly of the sciatic and femoral nerves.

Hematology, routine clinical serum chemistry and urinalysis showed no significant changes. Blood cholinesterase levels were depressed from normal.

The entire clinical picture in cattle poisonings suggests TOCP or other TAP/AAPs as the toxic agents. But, interestingly, a clinical report from the Ontario Veterinary College, on one of the heifers affected by the Barrie pipeline spill, showed no detectable TOCP levels in sciatic nerve samples, with a lower detection limit of the assay of 0.02 ppm.[57]

Recovery was observed in cases of less severe delayed neurotoxicity. This extended to normal calf production in the year following an intoxication event. There does not appear to be a latent teratogenic effect, nor a major effect on productivity during the poisoning. A number of cows calved during and just prior to the illness and those that were not paralysed to the point of being unable to stand, nursed their calves normally. In cases of decreased milk production, the calf growth rate tended to be slower. None of the nursing calves was affected. This suggests little or no transfer of the active toxicant from cow to calf by way of milk, but is an area of TAP/AAP effects which requires further investigation.

Although it is not possible to establish the doses of hydraulic fluid compounds which the cattle ingested or to which they were otherwise exposed, it does appear that cattle are particularly sensitive to TAP/AAP intoxication. They show a pattern of delayed neurotoxicity which parallels that of chickens and humans. It is worth noting that cattle appear to have an "insatiable" desire for oily substances not shown by other farm animals.[70]

Experimental acute studies have been carried out on livestock in order to describe the toxicity effects noted after such accidental contamination. Calves were acutely susceptible to Fyrquel 150 when given at oral doses of 5, 10, and 20 g/kg for ten equal doses, or when 5 g/kg was given as a single dose.[93] Initial signs of poisoning one day after dosing were diarrhea, abdominal pain, rapid respiration, and miosis. These signs increased in severity to a comatose state and the calves died in convulsions on the 13th day. When two cows were administered oral doses of Fyrquel 150 at 0. 5 and 1 g/kg, the initial signs were similar, and abated within two days.[93] The cows were clinically normal between days 7 and 19, and 7 and 14 after dosing with 0. 5 and 1 g/kg, respectively. From days 19 and 14 on, a progressive posterior motor paralysis set in and was complete by one week. Blood cholinesterase levels decreased markedly in all dosed cattle. Post-mortem examination of tissues showed axonal degeneration which apparently preceded a myelin degeneration.

A further laboratory study determined that at single oral dose levels of Cellulube 220 of 5 g/kg or greater, rabbits, goats and calves all developed signs of triaryl phosphate poisoning.[94] Signs of intoxication were observed four to 25 days after the administration of triaryl phosphate, or even by 24 hours at doses in rabbits of 20 g/kg or more. Anorexia, salivation, diarrhea, tympanites, dyspnea, incoordination and paralysis, and death, were observed signs of intoxication. Blood cholinesterase was inhibited, but enzyme inhibition was not necessarily correlated with the physical condition of the individual animal. No gross lesions were found, but microscopic pathology showed demyelination and axon swelling in the peripheral nervous system. A distinctive vacuolation of the cytoplasm of large neurons of the ventral motor nucleus of the spinal cord was observed in goats and calves.

It is apparent that no simple comprehensive statement can be made about the acute toxicity of TAP/AAPs. Their sub-lethal and lethal effects levels are very dependent on the specific individual chemical. This ranges from a very low dose acute toxicity of a fraction of a ppm, such as is the case for TOCP, to a much higher dose necessary to observe acute toxicity, such as seen for NPDP. The varied acute responses recorded for different formulations of TAP/AAPs express the toxicity characteristics of their component chemicals.

A further consideration of the acute studies is that a longer term assessment than the standard 96 hour limit is indicated. This is suggested by findings that lethality may be delayed and even follow a period of several days of apparent recovery.

5.2.2.2 Chronic toxicity: Again, the most comprehensive record of the chronic effects of TAP/AAPs exists for fish (Tables 5-3, 5-4), particularly the rainbow trout which appears to be the most sensitive species examined by Mayer et al.[43] Without accounting for dose, consistent morphological effects of TAP/AAP dosing are reduction in growth, reduction in vertebral collagen or spinal abnormalities, enlarged livers, and eye disorders.[43,65,83,85,92] The typical nervous degeneration has not been documented in fish experimentation. Behaviourally, however, there may be some nervous dysfunction in that fish do show decreased feeding activity, and perhaps increased hypersensitivity to light. Terminally, swimming patterns become abnormal and erratic.[43,65] A further morphological effect observed has been a bluish discolouration of the peritoneal lining and of fatty tissues.[65,85] No reproductive abnormalities are recorded, but it should be noted that much of the toxicity assessment carried out in the chronic studies either did not test for such an effect, or else could not have been observed because immature animals were used, such as trout fry.

Chemical pathology indicates probable liver damage in rainbow trout by elevations in plasma GOT, and muscle pathology by elevations in the muscle isozyme of LDH.[83] Decreases in blood cell parameters, particularly hematocrit, have been recorded by Wageman *et al*[65] and Hodson *et al*.[92]

Chronic doses may have an ultimately lethal effect, at least in a proportion of the fish examined.[43, 65, 92] Recovery appears to be possible with cessation of the intoxication.[65]

A further point which needs to be made with regard to TAP/AAP toxicity is that decreased serum acetylcholinesterase levels have been recorded,[65] although the same research group in a later publication on the same experiment[83] found no significant difference in serum acetylcholinesterase. In any case, the fluctuations in levels of this enzyme are no longer considered to be a good index of organophosphate intoxication (see Section 5. 3).

In a comparison among the different fish species examined, it is evident that the rainbow trout is the most sensitive species, markedly more so than fathead minnows.[43] The responses of lake trout are very similar to those of rainbow trout, suggesting some kind of uniform sensitivity among salmonids. When compared to other species, major differences are seen in trout and invertebrates, insofar as the latter are

TABLE 5-3 Chronic Toxicity Effects of Triaryl/alkyl Phosphates in Selected Species

Species	Compound	Dose		Behaviour & Signs	Growth
		Amount	Regime		
Rainbow trout (Salmo gairdneri)	IMOL -140	900 µg/L	10 L/min for 4-5 mo. (may have ingested some additionally)	Decreased feeding (particularly at surface) by 8 d, terminally abnormal swimming pattern	Continued
	Pydraul 50E	2 to 192 µg/L	Flow-through for 90-days (trout fry)		Increased at 2 µg/L, decreased at 3 to 192 µg/L
	TPP	1 to 10,000 µg/g food	In diet for 6 mo.	Abnormal swimming pattern at highest dose	Decreased at highest dose
Birds - duck	TAP's			Mild sensory disturbances and motor weakness	
- pheasant	AAP's				
Pig	TOCP	128 mg/kg body weight	percutaneous injection on thorax every 48 hr. 83 times	gradual development of irreversible posterior paresis from 70 to 166 days of exposure	decreased weight gain by 100 days

TABLE 5-3 (continuation)

Observed Effects					
Clinical Chemistry	Hematology	Pathology	Lethality	Recovery	References
LDH and GOT increased, AlkPhos decreased	Decreased hematocrit	Enlarged livers, darkly-coloured fatty tissues (blue-grey)	Up to 50% by 4 mo.	Yes	43, 65
Whole body proline, hydrooxyproline and vitamin C increased; vertebral collagen, calcium and phosphorus reduced		Abdomens distended; abnormal colouration; hemorrhagic areas; smaller eyes and eye cataracts by 30 d.			85
Plasma protein increased at highest dose	Slight decrease in hematocrit, RBC No., and RBC vol.	Increased hepatosomatic index at high dose, major vertebral and body deformations	50% at highest		92
		Nervous degeneration progressive from legs to wings, starting at 8-12 days post-dose	Yes	Yes, after 3 weeks post-dose; complete only in mild cases	96
		Demyelination of spinal cord		No	97

TABLE 5-4 Concentrations (µg/L) of Triaryl/alkyl Phosphate Exposure in Water Causing Significant ($P < 0.05$) Chronic Toxicity Effects[43]

Species and Compound	Length of Exposure	Survival	Growth	Cataracts	Vertebral Collagen
Daphnids[a]	28 days				
Pydraul 50E		>136			
Midge[b]	30 days				
Pydraul 50E		>130 <290			
Rainbow trout	90 days				
Pydraul 50E		>8 <15	>2.5 <3.5	>1.1 <2.5	>0.82 <1.1
Pydraul 115E		>8.4 <16	<5.8	<5.8	>5.8 <8.4
TPP		>1.4	>1.4	>1.4	>1.4
NPDP		>4.2	>4.2	>1.6 <2.1	>0.36 <0.75
CPDP		>2.0	>1.4 <2.0	>0.76 <1.4	<0.22
Lake Trout	120 days				
Pydraul 50E		>5.3 <16	> 2.6 <5.3	>2.6 <5.3	<2.6
Fathead minnows	30 and 90 days				
Pydraul 50E		>560 <752	>560 <752	>138 <317	
TPP		>87 <230	>230	>230	

[a] No reproductive effects were observed at or below 136 µg/L.

[b] Study on midge (*Chironomous plumosus*) emergence: Sanders 1979, personal communication to Mayer *et al*.[43]

much more lethality resistant. Birds such as ducks and pheasants, show a toxicity response similar to that recorded in hens (see Section 5.3) with a progressive nervous degeneration being predominant.[96,98] This is a delayed response and may develop to involve both legs and wings. Recovery was possible in mild cases. In the pig a chronic percutaneous administration of TOCP resulted in spinal cord demyelination and associated irreversible posterior paresis[97]

It would seem that the route of administration has a bearing on the severity of toxicity effects. Rainbow trout, for instance, are sensitive to TPP, resulting in mortality at concentrations in water greater than 1.4 µg/L.[43] When dosed orally, mortalities resulted only at a TPP concentration in food of 10,000 µg/g (or greater than 1000 µg/g given the experimental protocol of the study).[92] Although it is not possible to make a definitive calculation of the amount of TPP absorbed by each route, it may be calculated speculatively, taking into consideration branchial chamber water flow and usual daily food consumption, that the toxicity is greater when TPP is dissolved in the water.

As in the acute experimental studies, the extent of a chronic toxicity response depends on the nature of the formulation of a TAP/AAP product, or the compound itself. The data presented in Tables 5-3 and 5-4 indicate that Pydraul 50E is more toxic than either IMOL S-140 or Pydraul 115E. This result is identical to that found in the acute studies (Table 5-2). Contrary to the acute studies, however, TPP was of the same general order of toxicity as the compounds NPDP and CPDP. The environmental significance of such comparative findings is that the effect of the contaminant is dependent on its source to the animal species. Food chain contamination has to be assessed differently from that of the ambient environment.

5.2.2.3 In vitro and culture studies: Studies of *in vitro* action, reductionist in scope and interest, have elucidated some of the basic actions of organophosphates. Most of such studies are typically carried out on laboratory species, as will be discussed in Section 5.3, but one study to date has dealt with more exotic experimental species. Detailed examination of the sarcoplasmic reticulum, that is, a unit of the cellular sub-structure of muscle cells derived from endoplasmic reticulum and associated with the contractile process, has revealed, in the skeletal muscle of the crab *Carcinus maenas* and the cockroach *Periplaneta americana*, shifts in Ca^{2+} dynamics under TCP influence at a concentration of 0.001 mole/L.[99] A major effect of TCP is a marked inhibition of the normal accumulation of Ca^{2+} by the sarcoplasmic reticulum. Additionally, the release of bound Ca^{2+} is promoted by TCP. The consequence of this action is an accumulation of Ca^{2+} in the myoplasm, directly influencing the contractile protein elements of the muscle cell and resulting in an induction of contraction.[99] It is interesting to note that while this TCP action results in an abnormal induction of the contractile state and presumably paralysis *in vivo*, this state has been achieved without involving acetylcholinesterase. Insofar as the modification of acetylcholinesterase titre has been unsatisfactorily associated with the action of TAP/AAPs, this *in vitro* study is particularly important in proposing an action of the toxicant at a biochemical level.

Culture studies of the capacity of micro-organisms and fungi to metabolize TAP/AAPs are of particular interest because such studies help to describe the environmental fate of these toxicants, as present in soil, for instance. While a number of species of mesophilic fungi of three common genera did not utilize the aryl phosphates TPP, TCP and TXP, nor a mixed AAP plasticizer,[100] a number of thermophilic fungi were able to use TPP and TCP as a metabolic and growth supporting substrate.[79, 101] These fungi showed a positive growth response to the TAP compounds not only in agar culture at 1% v/v phosphate ester, but also in soil at 1.5 mL phosphate ester per 3 g soil. The environmental considerations of such findings are significant, even if the fungi do not necessarily degrade the TAP compounds,[101] but only support the fungal growth. In the case of *Aspergillus niger*, for instance, it is of interest to note that this fungus was not affected by TPP, or its hydrolysis product phenol at 5×10^{-5} to 5×10^{-3} M.[102]

5.2.2.4 Nutritional relationships: A number of studies of the effects of TAP/AAPs have indicated a relationship to the nutrient status and dietary requirements of the test population. Although only a minimal amount of this work has dealt with non-laboratory species, it should be noted that as early as 1952, Draper *et al* found that the addition of TOCP to a vitamin E-deficient diet resulted in the paralysis of the hind legs of lambs.[103] The authors thought that TOCP acted as a direct antagonist to vitamin E, promoting the muscular dystrophy induced by a dietary deficiency in the vitamin. These findings received some clarification later by the work of Cowlishaw and Blaxter on calves,[104] which determined that while TOCP antagonizes the action of dietary vitamin E by interfering with its absorption from the gut, TOCP exerts its main action directly, that being a demyelination of motor nerves and consequent neurological disturbance of muscle function.

5.2.2.5 Organophosphate potentiation: One of the areas of research on TAP/AAP toxicity has emphasized the potential of these chemicals to potentiate, that is, increase the relative toxication, of other organophosphates. Malathion, a widely used insecticide has received major attention. A potentiation of malathion toxicity by the synergistic action of TAPs tested at pesticide/TAP ratios of 1:1 to 1:20, has been well documented in the house-fly, (Musca domestica), and the red flour beetle (Tribolium castaneum), as well as in mosquito and leafhopper species.[88-90,102,105] Generally, those strains which developed a resistance to the insecticide malathion by the specific induction of a carboxyesterase enzyme which detoxified malathion were potentiated by TAPs such as TPP and other organophosphates. The TAP/AAPs, when administered by themselves, were generally not toxic to the insects at the compounds' synergistic level of concentration. Carbaryl was similarly potentiated by TPP, at a 1:5 pesticide/TPP ratio, in tobacco cutworms.[102] Eto et al showed in the house-fly that esterase activity was responsible for the hydroxylation of TPP to TPP-OH.[105] It is this competitive inhibition for substrate by TPP which decreases the enzyme activity for malathion and potentiates its effect. By comparison and explanation, those insects not dependent on carboxyesterase induction to be malathion resistant were not potentiated by TPP and TOCP.[91]

Potentiation of malathion toxicity has also been demonstrated in a number of non-insect species. Sunfish, Lepomis gibbosus, and bullheads, Ictaluras melas, showed inhibited liver carboxyesterase activity when injected with TOCP at 125 mg/kg body weight, although brain cholinesterase activity stayed the same.[106] This resulted in a marked enhancement of brain anticholinesterase activity by subsequent malathion administration or a potentiation of 11- to 12-fold of malathion toxicity measured by this index. The same authors also established a 100-fold potentiation, by TOCP at 125 mg/kg body weight, of malathion by TOCP anticholinesterase activity in brain tissue of the leopard frog, Rana pipiens, and by 17-fold in the quail, Coturnix sp.

The potentiation effects by TAP/AAPs of organophosphate insecticide toxicity are of interest from a practical standpoint of creating more effective insecticides by using TAP/AAP carriers. A further consideration is that an assessment of the environmental toxicity of the TAP/AAPs must then take into account the organophosphate load in an affected species. This is particularly so if the species is a non-target species for the insecticide application.

5.3 PHARMACOTOXICOLOGY

5.3.1 Pharmacodynamics

Although the route of exposure and absorption of a toxicant usually relates to the expression of its toxicity effects, this aspect has received little attention in the case of TAP/AAPs. An early study by Gross and Grosse[107] tested the relative toxicities of ortho-, para-, and meta-isomers of TCP, as well as their absorption characteristics through mucous, peritoneal, and epidermal membranes. Para- and meta-TCP were only poorly or not at all absorbed by these routes. This was not, however, the cause of their innocuous character in this study, since they were also harmless when injected. Tri-o-cresyl phosphate, on the other hand, showed a ready absorption across body membranes. Following subcutaneous injection, the p- and m-forms were slowly excreted over several weeks by way of the bile. An i. v. injection, however, resulted in a substantial and rapid excretion by bile. The authors used chemical assays for the determination of cresol and phosphoric acid, and were not able to detect the formation of free cresol in excretion and elimination processes. The assay was not sensitive, however, to the presence of conjugated cresols, which may have been excreted by way of the urine and the feces. Cresyl esters were identified in rabbit and dog urine.

One of the few experiments reported on humans was that of Hodge and Sterner[108] who dermally dosed themselves and a dog with ^{32}P-labelled TOCP and then measured blood, urine and dog tissue samples for radioactivity. They found that absorption into plasma in humans was very rapid, as was excretion in the urine. Dermal absorption of TOCP in humans exceeded that in the dog about 100 times. In both cases, the radiolabel disappeared from the plasma very rapidly within 24 hours. A more recent study using radiotracers (^{32}P-TOCP) showed that in chickens, as well, there was a rapid absorption, in this case from the gut, and subsequent rapid clearance of the label from the plasma.[109, 110] In both dosing studies, a proportion of the labelled TOCP was excreted by way of the urine; as much as 26.5% of the administered oral dose in chickens was excreted over 72 hours, 99% of this loss as unmetabolized TOCP. Much of the rest of the TOCP dose is stored in body tissues and converted to a predominant metabolite such as the cyclic saligenin in the chicken,[109,110] and more specifically in the rat to 2-(o-cresyl)-4H-1:3:2-benzodioxaphosphoran-2-one.[111] The metabolites have been identified as having antiesterase activity, and may even be more potent toxicants than TOCP.[112]

Although a significant proportion of a TOCP dose disappears from the plasma by its excretion in native or metabolized form, a larger portion of the TOCP dose appears to be stored in tissues. Gross and Grosse identified liver and spleen to be the sites of retention of TCP compounds from various routes of exposure.[107] Dermal absorption in the dog showed accumulation, in order of increasing concentration, in visceral organs, muscle, brain and bone.[108] In the chicken, the liver particularly has been identified as the organ sequestering TOCP from circulation to rapidly clear the plasma of the TAP.[109,110] The liver is then identified as a major site of TAP metabolism, including the formation of a toxic metabolite also capable of inducing effects characteristic of TOCP.[112]

5. 3. 2 Toxicity Effects

5. 3. 2. 1 Acute toxicity: As a class, the TAP/AAPs have to be considered as only weak acute toxicants. As indicated by LD_{50} values presented in summary Table 5-5, exceptionally large doses, of the order of several grams per kilogram of body weight, are generally necessary to cause death. Of these, the TOCP compound is the most acutely toxic, followed by DBPP. In cases of acute toxicity, the cause of the effect appears to be distinct from the more

TABLE 5-5 Summary Toxicity Record for Triaryl/alkyl Phosphates in Pharmacotoxicological Studies

Compound	Species	Route	Total Dose, Single or Cumulative (g/kg) LD$_{50}$	TD$_o$	TD$_{min}$	TD$_{50}$	References
TPP	cat	i.p.			0.1	0.4	94, 107 113,114
				0.3	0.2		72
		s.c.		>0.4			115
			>0.2	0.1	0.2		114
	chicken	oral	>5	60			113
				0.5-2.0			114
				1.0			116
				25			117
				0.7			118, 119
	guinea pig	oral		>4			72
		s.c.		>3			72
	mouse	oral		>3			72
		s.c.		>3			72
	monkey	s.c.		0.5			120
	rabbit	dermal	10.8				113
		oral		>1.0			121
	rat	oral	>7.94				72, 113
		s.c.	>3.0				72
TCP-mixed	chicken	oral	>10		>10		113
					0.05		116
	rabbit	oral			5		94
		dermal	>7.94				113
	rat	oral	>15.8				113
TOCP	cat		>0.3-0.5				107
	chicken	oral				0.42	113
						0.05	116
						0.25	118, 119
		dermal			0.06		116
					>0.05		122
	dog	s.c., CNS	>0.1				107
					<0.03		114
	dog	intraneural		0.02			114
	guinea pig		0.3-0.5				107
	mouse		0.28				108
	rabbit	dermal	>0.1				107
	rabbit				3.7		113
	rat	oral			8.4		113
TCP-para	chicken	oral	5.0				116
			1.2				118, 119
	rat	oral		270			123
TCP-meta	chicken	oral	5.0				116
			1.2				118, 119
	rat	oral	>270				123
TXP-2,4-xylenyl	chicken	oral	>1	12.0			113
				2.5			116
	rabbit	dermal	>7.94				113
	rat	oral	>15.8				113

TABLE 5-5 (cont'd.)

			Total Dose, Single or Cumulative (g/kg)				
Compound	Species	Route	LD_{50}	TD_o	TD_{min}	TD_{50}	References
TXP 2,5-xylenyl	chicken	oral		2.5			116
TXP 2,6-xylenyl	chicken	oral	>1	12.0			113
				2.5			116
	rabbit	dermal	>7.94				113
	rat	oral	>15.8				113
TXP 3,5-xylenyl	chicken	oral		2.5			116
CDP	chicken	oral				1.23	113
			>10	120			113
						<1.0	116
					0.5		124
						0.12	118, 119
	rabbit	dermal	>5				113
	rat	oral	10.4				113
o-IPDP	chicken	oral				10.2	113
					1.2		118, 119
	rabbit	dermal	>5				113
	rat	oral	10				113
p-IPDP	chicken	oral	>10	120			113
mixed-IPDP	chicken	dermal		>4.25			122
Di-o-isopropyl phenyl	chicken	oral			1.2		118, 119
Di-p-isopropyl phenyl	chicken	oral		1.0			118, 119
DBPP	chicken	oral	<2	2.68			113
	rabbit	dermal	<5				113
	rat	oral	2.4				113
EHDP	chicken	oral	>10	120			113
	rabbit	dermal	>7.94				113
	rat	oral	>15.8				113
IDDP	chicken	oral	>10	120			113
	rabbit	dermal	>7.94				113
	rat	oral	>15.8				113

NOTE: LD_{50}, median lethal dose; TD_o, highest dose reported with no delayed toxic effect; TD_{min}, minimum dose reported with a delayed toxic effect; TD_{50}, median toxic dose producing delayed toxic effects.

delayed or chronic responses, and is likely a direct antiesterase activity, leading to acute incoordination, paralysis, dyspnea, and death.

5.3.2.2 Delayed neurotoxicity: The more common toxicity response recorded for TAP/AAP intoxication is one of delayed neurotoxocity, with no initial poisoning effects. In general, among the mammalian species examined, this commences one to two weeks after dosing, with a flaccid paralysis and ataxia of the rear limbs, progressing to the forelimbs and perhaps involving the trunk neuro-musculature in severe cases. With trunk paralysis, death may result from ineffective breathing actions leading to dyspnea. In all cases examined, the doses appear to be strictly cumulative and in that sense chronic exposure assessments are not separable.

As indicated in Table 5-5, it is again the TOCP which shows the most marked delayed toxicity effect. Most of the comparative information has to be drawn from studies on chickens, where calculations of median toxic doses, at which 50% of the experimental population showed delayed neurotoxic effects, give TD_{50} values for TOCP of 0.05 to 0.42 g/kg body weight. Values for CDP follow with a range of 0.12 to 1.23 g/kg, and, comparatively, ortho-IPDP at 10.2 g/kg. The toxic doses required to have a minimum response in the experimental population (TD_{min}) show a similar relationship and strengthen the point that TOCP is the most toxic of the group of TAP/AAPs under investigation. A point of additional interest, one which has undoubtedly caused many problems in the interpretation of experimental dose-related results, is that the maximum values of concentration at which no effects were noted in at least one individual of the population (TD_o)

were at times extremely high. This is perhaps due to a great range of individual susceptibility and creates a large experimental variability. In summary, however, it can be stated that there are defined structural characteristics associated with the expression of the toxicity effect. It is generally agreed that a delayed neurotoxicity effect requires a TAP/AAP compound of an ortho- or para-substitution with at least one or two hydrogen atoms on the alpha-carbon, respectively.[113,119] Ortho-sbustitutions are the most effective,[114] and meta-substitutions do not appear to be neurotoxic. Structural aspects pertinent to toxicity will be discussed in detail in Section 5. 3. 3. 1.

Comparative toxicity information is available for mammalian species. In general, they are less sensitive to TAP/AAP intoxication than chickens and also do not mimic human responses as well as do the birds. An exception may be the cat, which appears to be fairly sensitive. Aside from the dose related studies referenced in Table 5-5, effects have also been reported in rabbits, rhesus monkeys, calves. cats, and dogs.[114, 125] Although their overall sensitivity is perhaps less, they again are most affected by TOCP. The apparent conflict which exists in the expression of TPP toxicity in the cat, where i. p. injections showed a marked toxicity of the same order as TOCP,[126] can be dismissed by attributing this effect to the presence of impurities in the compound.[118] (An examination of TPP resistance in chickens shown in Table 5-5 also suggests such an inconsistency.) A repeat of the experiment with cats, using pure synthetic TPP showed no neurotoxicity at any dose.[115] It has to be considered, in any case, that some of the reported toxicities for individual TAP/AAPs may be misleading in that extremely pure compounds were difficult or impossible to obtain. A pervasive contaminant is TOCP, which may thus account for the effects observed. A further complicating factor may be the suggestion made by Johnson,[118, 119] who found a marked CDP toxicity in chickens, that this compound may be more toxic than the tri-cresyl compound.

Special mention must be made of the effort of the Stauffer Chemical Company to define the comparative toxicities of a number of TAPs in selected laboratory test species. This information, made available to the authors of this report by Stauffer Chemical Company,[127] is presented in summary in Table 5-6. The studies are generally of an acute nature. The acute lethal oral, dermal, or inhalation concentrations were generally of the same order of magnitude for all compounds tested, although IPDP appeared to be most acutely lethal. Minor differences were found in limited primary skin and eye irritation. The Phosflex Z formulation was found to be an eye irritant and is classified as corrosive. Although IPDP was more acutely toxic, TCP showed the greatest neurotoxicity in chickens. Further, although only mildly neurotoxic, expressed as a TOCP% equivalent, IPDP gave a positive neurotoxic esterase assay. A possible age effect is indicated here in that younger chickens were slightly more neurotoxically sensitive to IPDP. The TCP tested was presumably a mixed isomer; and may have included TOCP. The overwhelming specific toxicity of TOCP was again well demonstrated in these tests. Stauffer also carried out carcinogenesis and mutagenesis testing on some of their compounds (these results are reported later in Section 5. 3. 4).

A small number of studies report neurotoxicity effects resulting from exposure to commercial TAP/AAP fluids. Cellulube 220 (containing TPP, TCP, TXP, trialkylphenylphosphate) given by inhalation as an aerosol mist showed chickens to be more affected than monkeys, rabbits or dogs.[128] Again, long term inhalation studies by Siegel et al of a TAP hydraulic fluid mist showed neurotoxicity in chickens at 23 to 110 mg/m^3 and rabbits at 102 to 103 mg/m^3 during the 90-day test period.[129] Dogs, rabbits and rats showed no effects at even the high concentration of 110 mg/m^3. Oral doses of Cellulube 220, from 2 to 60 g/kg, gave a different species response, in that rats and chickens showed little effect while rabbits, goats and calves were more susceptible.[94] Although one may wish to draw dose-route or species specific inferences from the above three studies this may perhaps be misleading when it is considered that even different batches of the same TCP-1 oil, found to be qualitatively and quantatively similar by infrared analysis, resulted in markedly different toxicity assessments.[130] When a TCP-1 hydraulic fluid was examined for toxicity by oral dosing in chickens, it was found to behave as if it contained 21% TOCP, although its nominal TOCP fraction was only 1.5% and the high TOCP activity equivalent was suggested to be the result of some other highly neurotoxic moiety, or that other components in the mixture potentiated TOCP paralytic activity.[131] Subcutaneous injection of TCP-1 in rabbits, mice, and dogs showed similar relationships. The neurotoxic effects from TCP-1 were qualitatively similar to those caused by TOCP. Carpenter et al also compared the effects of different dosing routes in rabbits;[131] TCP-1 was administered subcutaneously, percutaneously, orally, and by inhalation of an aerosol. The aerosol dosing was potentially the most toxic, with a

TABLE 5-6 Summary of Toxicology Data as Provided by Stauffer Chemical Company on Triaryl Phosphates[127]

Compound	Species	Test	Result
TCP	rat, male	acute oral LD_{50}	>4.64 g/kg
	rabbit	acute dermal LD_{50}	>4.64 g/kg
		primary skin irritation (4 hr. exp.)	non-irritant
		acute primary eye irritation	non-irritant
	chicken, hen	neurotoxicity, oral dosing	18.7 to 25.1 TOCP% equivalent*
TXP	rat, male and female	acute oral LD_{50}	>10.00 g/kg
	male		>4.64 g/kg
	male and female	acute inhalation LC_{50}	>8.6 mg/L/hr <66.6 mg/L/hr (nominal conc.)
	rabbit	acute dermal LD_{50}	>2.00 g/kg >4.64 g/kg
		primary skin irritation - 4 hr. exp.	non-irritant
		- 24 hr. exp.	mild irritant
		acute primary eye irritation	non-irritant
	chicken, hen	neurotoxicity, oral dosing	9.4 and 18.7 TOCP% equivalent*
IPDP	rat, male	acute oral LD_{50}	>4.64 g/kg >5.00 g/kg
	female		>2.00 g/kg >2.53 g/kg
		acute inhalation	>5.20 mg/L/hr
	rabbit, male and female	acute dermal LD_{50}	>4.64 g/kg
	male and female		>2.00 g/kg
		primary skin irritation - 4 hr. exp.	non- to moderate irritant
		- 24 hr. exp.	mild irritant
		acute primary eye irritation	non-irritant

TABLE 5-6 (cont'd.)

Compound	Species	Test	Result
IPDP (cont'd)	chicken, hen 12 to 13.5 mos.	neurotoxicity, oral dosing	0.0 TOCP% equivalent*
	chicken, hen 3.5 to 5 mos.		0.4 TOCP% equivalent*
		neurotoxic esterase assay	positive
BPDP	rat	acute oral LD_{50}	>4.64 g/kg
	male and female		>5.00 g/kg
		acute inhalation LC_{50}	>15.7 mg/L/hr nominal >18.9 mg/L/hr nominal 3.1 mg/L/hr
	rabbit	primary skin irritation	
		- 4 hr. exp.	non-irritant
		- 24 hr. exp.	mild irritant
		acute dermal LD_{50}	>4.64 g/kg >2.00 g/kg
		acute primary eye irritation	non- to mild irritant
	chicken, hen	neurotoxicity, oral dosing	0.0 to 0.4 TOCP% equivalent*
		neurotoxic esterase assay	negative
mixed TAP (Phosflex Z)	rat, male	acute oral LD_{50}	>4.04 g/kg
	rabbit	acute dermal LD_{50}	>4.04 g/kg
		primary skin irritation - 4 hr. exp.	non-irritant
		acute primary eye irritation	corrosive
	chicken, hen	neurotoxicity	0.0 TOCP% equivalent*

*TOCP% equivalent is calculated as follows:

$$\frac{(\text{dose TOCP as positive control})}{(\text{dose tested material})} \times \frac{(\text{total paralysis point score for tested material})}{(\text{total paralysis point score for TOCP as positive control})} \times 100$$

lethal dose at 1 gm/kg body weight. A low dose, 2 mg/L for 1 to 2 hours per day was tolerated, however, with no significant physical effects. A subcutaneous dose required to cause death was of the order of 10-15 g/kg. Application of TCP-1 to 100 cm^2 of skin for four hours daily equalled the effect of 0.36 g/kg per day subcutaneously. Based on these experiments in rabbits, the route of administration certainly is of significance in the expression of toxicity. A limited amount of information is available for Reofos (a "synthetic" TAP free of orthocresylphosphates and of alkylphenol derivatives) which was shown to have only minimal neurotoxicity and no dermal effect in chickens and rats, as compared to TXP. A rat LD_{50} of ≥ 17 g/kg was found.[132]

Assessment of the delayed neurotoxocity studies on formulated TAP/AAPs shows that the complexity of the formulation, diversity of dosing regimes, and differences among species emphasizes the need for controlled studies on pure compounds. The establishment of accepted baselines with single compounds of toxicological interest may then lead to an examination of potentiation and synergistic neurotoxic actions in mixtures.

5.3.2.3 Neuropathology: The delayed neurotoxicity resulting from TAP/AAP intoxication is typically associated with lesions in the distal parts of the long central and peripheral nerve fibre tracts, characterized by a nerve fibre degeneration. This can be classified as a central-peripheral distal axonopathy.[133] The condition has been associated with TOCP poisoning for a long time in humans[134] and received considerable attention in that it explains the most overt symptom of poisoning, that of ataxia and motor paralysis, particularly of the hind limbs.

Primary neural lesions were identified in the cat as a result of experimental TPP and TOCP exposure.[114, 120] (There may be some question of the purity of the TPP used in these experiments in view of its probable TOCP contamination.) The neurologic symptoms evident several days after poisoning were associated with degeneration of motor neurons in the lumbar and cervical regions of the spinal cord. It has been suggested that degeneration of nerve cells is associated with acute poisoning, while sub-acute poisoning is associated with a degeneration of peripheral nerves only. The former can be considered irreversible in effect, while the latter damage can be repaired. Sub-acute delayed neurotoxicity has been shown to be recoverable in many species. Smith and Lillie first reported studies on dogs, monkeys, cats, and chickens which showed degeneration of the myelin sheaths of the peripheral nerves, and in some cases degeneration of the anterior motor horn neurons of the spinal cord.[120] Such a progression explained the initiation of paralysis in the hind limbs and its involvement of anterior limbs and trunk musculature in more severe cases.

The mechanisms underlying the progressive paralysis have been extensively investigated in order to describe the pathology functionally. Electrical stimulation of motor nerves in poisoned chickens showed that the muscle fibre and the neuromuscular synapse were not affected, but motor neuron conduction velocity was decreased as may be anticipated in view of the myelin-sheath damage.[114] Further, demyelination of central and peripheral motor neurons was not associated with any anticholinesterase activity, as concluded for TOCP and other organophosphorus compounds causing demyelination.[135,136] Antiesterase activity of TAP/AAPs will be discussed in detail in the following section. The motor nerve lesions were similar to those of vitamin B (thiamine) deficiency.[135,136] The neural defect does not appear to relate to the metabolic functions of the nervous system as far as phospholipids are concerned. Paralytic demyelinating doses of TOCP were shown to have no effect on the incorporation of ^{32}P into nervous system phospholipids in the afflicted chicken.[137] In the spinal cord of the cat, however, significant differences in the lipid phosphorus content were observed in TOCP treated animals.[138] Taranova and colleagues have recently determined changes in lipid composition and metabolism in guinea pig CNS as a result of TOCP intoxication.[139-142] The resultant neuroparalysis resulted in an accumulation of cholesterol esters in brain stem and spinal cord as a probable result of myelin degradation. Galactolipid and ganglioside changes in spinal cord and brain stem were attributed to alterations in neuron structure. Cerebroside, ganglioside, phospholipid, and cholesterol metabolism was depressed, indicating alterations in neuron and oligodendrocyte metabolism as a result of TOCP intoxication.

Research by Cavanagh on TOCP poisoning in cats has emphasized a direct relationship of peripheral nerve damage to nerve fibre length and diameter, in particular, similar to that in chickens.[143] The particular susceptibility of large diameter fibres has been verified in chickens by Krinke _et al_.[144]

The affected nerve axons "die back" towards the cell body.

Degeneration in the projection areas of most long ascending and descending spinal tracts was noted in TOCP poisoned cats, but here in the CNS, fibre length and not diameter seemed to be important in determining the severity of the lesion.[145] Although some differences were noted in the spinal cord degeneration patterns in the chicken and cat after TOCP poisoning,[146] it seems that the neuronal and spinal tract degeneration are causally related, thus bringing the morphology of TOCP neurotoxicity in line with a Wallerian degeneration.[147]

Whereas demyelination is a readily recognized neural effect, it does not appear to be the primary lesion. Ultrastructural examinations in TOCP treated experimental animals have verified this sequence. In the TOCP poisoned cat, there is an accumulation of abnormal membrane-bound vesicles and tubules within an otherwise normal axoplasm of small myelinated motor nerve terminals in the foot muscles and in small myelinated fibres in the spinal cord, starting a week or more prior to the onset of clinical signs.[148] The onset of neurological signs was associated with unusual lamellated bodies in the neuromuscular junctions, muscle fibres, and in spinal cord anterior horn boutons terminaux. Endoplasmic reticulum changes were noted at early stages. Myelin destruction was a later event and was associated with severe degenerative changes within the axoplasm. Similarly early axoplasm changes have been noted in TOCP treated chickens.[149] Both myelinated and non-myelinated axons were affected. Ultrastructural examination of the axon-Schwann cell (myelin sheath) compound membrane shows a discontinuous closure of the normal intercellular gap, suggesting a structural alteration of adjacent membranes. Another early effect prior to neurological signs or microscopic changes is that myelin lipid changes occur soon after poisoning.[170]

Neural lesions in experimental laboratory animals closely resemble those noted in poisoned humans. In all cases, the onset of neurological signs is associated with microscopic damage of both the axon and myelin sheath. Progressive ultrastructural and pathological changes are recorded prior to the signs of paralysis, however, and suggest that axoplasmic changes precede and perhaps causally relate to secondary myelin changes.

5.3.3 Mechanism of Action

5.3.3.1 Structure-activity relationships: Based directly on the diversity of TAP/AAPs examined experimentally, it is now possible to establish a toxicity series which will be predictive in attributing the degree of toxicity to specific structural configurations. A direct comparative study in guinea pigs injected subcutaneously with TAPs showed the following relationship, listed in decreasing order of neurotoxicity: TCP (37% ortho), CDP, TCP (2% ortho) and TXPs, with the TXPs being non-toxic.[150] Similar series can be constructed with reference to Table 5-5. A more detailed and exhaustive assessment of native compounds had been carried out by Henschler and colleagues. Both TCP and TXP compounds could be ordered by their neurotoxicities to chickens in that esters with one ortho-isomer were more potent than those with two, and these more potent than those with three ortho-isomers. Mono-ortho-CDP was found to be the most toxic single TAP.[15, 151] The ortho-configuration was the most potent in any case, more so than meta- and para- substitutions.

A more detailed structure-specific summary has been presented by Eto in his 1974 treatise on organophosphorus pesticides.[152] Table 5-7, taken from Eto's work, shows that all neurotoxic TAP/AAPs contain at least one o-alkylphenyl ester group. The compounds tri-p-ethylphenyl and p-ethylphenyl diphenyl phosphates are notable exceptions.

Johannsen et al also determined the neurotoxic potential of a series of triaryl, trialkyl and tri-(alkyl aryl) phosphates in chickens.[113] Quantification of dose-neurotoxic response relationships identified three active compounds, TCP, CDP, and o-IPDP, differing in neurotoxic potential. In contrast to the statement by Aldridge et al[154] that in TAPs there is no apparent relationship between structure and activity, a number of important conclusions about structure-activity relationships can be drawn, summarized by Johannsen et al as follows:[113]

1) Phosphates prepared from o-alkyl-substituted phenols frequently are neurotoxic; however, the o-alkyl group must contain at least one hydrogen atom on the α-carbon for activation.

2) The neurotoxic potency of active o-alkyl-substituted phosphates declines with increased mass and branching of the o-substituent.

3) Neurotoxicity is reduced by further substitution in the ring already containing an o-substituent.

4) A series of unsymmetrical phosphates containing an alkyl group in the p-position of one ring are not neurotoxic even though they contain hydrogen atoms on the α-carbon.

TABLE 5-7 Structure and Neurotoxicity of Triaryl Phosphates (from a summary by Eto[152])

R	R'	R''	Dose mg/kg	Neurotoxicity
H	H	H	1,000	-
2-Me	H	H	50	+
2-Me	2-Me	2-Me	25 to 200	+
2-Me	2-Me	3-Me	250	+
2-Me	2-Me	4-Me	25	+
2-Me	3-Me	3-Me	100	+
2-Me	3-Me	4-Me	100	+
2-Me	4-Me	4-Me	50	+
2-Me	3,5-diMe	3,5-diMe	1,000	+
2-Et	H	H	1,000	+
2-Et	4-Me	4-Me	200	+
2-Et	2-Et	H	250	+
2-Et	2-Et	4-Me	500	+
2-Et	2-Et	2-Et	500 x 5	+
2-Et	3,5-diMe	3,5-diMe	500	+
2-n-Pr	4-Et	4-Et	200	+
2-n-Pr	2-n-Pr	4-Me	1,000	+
2-n-Pr	2-n-Pr	2-n-Pr	1,000	-
2-n-Pr	3,5-diMe	3,5-diMe	1,000	-
2,3-diMe	2,3-diMe	2,3-diMe	4,250	+
2,4-diMe	2,4-diMe	2,4-diMe	2,000	+
2,4-diMe	2,4-diMe	3,5-diMe	10,400	+
2,5-diMe	2,5-diMe	2,5-diMe	1,000	-
2,6-diMe	2,6-diMe	2,6-diMe	1,000	-
2,6-diMe	3,5-diMe	3,5-diMe	24,000	+
2-Me-4-Et	2-Me-4-Et	2-Me-4-Et	500	-
3-Me	3-Me	3-Me	5,000	-
3-Et	3-Et	3-Et	1,000	-
4-Me	4-Me	4-Me	5,000	-
4-Et	4-Et	H	2,000	-
4-Et	4-Et	4-Et	200 to 1,000	+
4-Et	4-Et	4-Me	500	-
4-Et	4-Me	4-Me	500 x 5	-
4-Et	H	H	1,000	+

NOTE: The triaryl phosphates are of the general formula:

$$\left[(\text{R-},\ \text{R}'\text{-},\ \text{R}''\text{-phenyl})\text{O}\right]_3\text{PO}$$

5) p-Tertiary-butylphenyl diphenyl phosphate, with no hydrogen on the α-carbon available for activation does not produce delayed neurotoxicity.

Applying this summary by Johannsen et al to toxicity data on the majority of the isomers of tricresyl phosphate reported by Klimmer and Schunk,[16] one can see excellent correlation (Table 5-9).

The mechanisms underlying structure-activity relationships generally invoke inhibition of an esterase as the initial event in the delayed neurotoxicity of organophosphorus compounds. Aldridge pointed out that all organophosphorus compounds producing ataxia are esters with a general capacity to inhibit esterases in vivo.[155] The discovery of TAP metabolites of marked anti-esterase activity has given further support to structure-activity relationships. Further, Aldridge found that a highly purified TOCP was not active in inhibiting cholinesterase in vitro.[155]

Casida et al[112] and Eto et al[111] have shown that in rats, in vitro and in vivo, TOCP is hydroxylated and cyclized by liver microsomes to form several products. The primary product was 2-(o-cresyl)-4H-1:3:2-benzodioxaphosphoran-2-one:

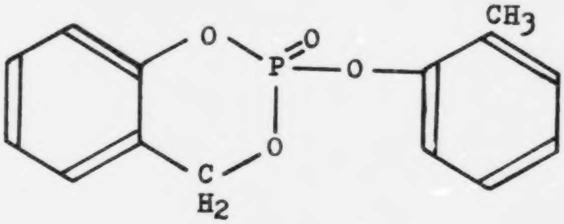
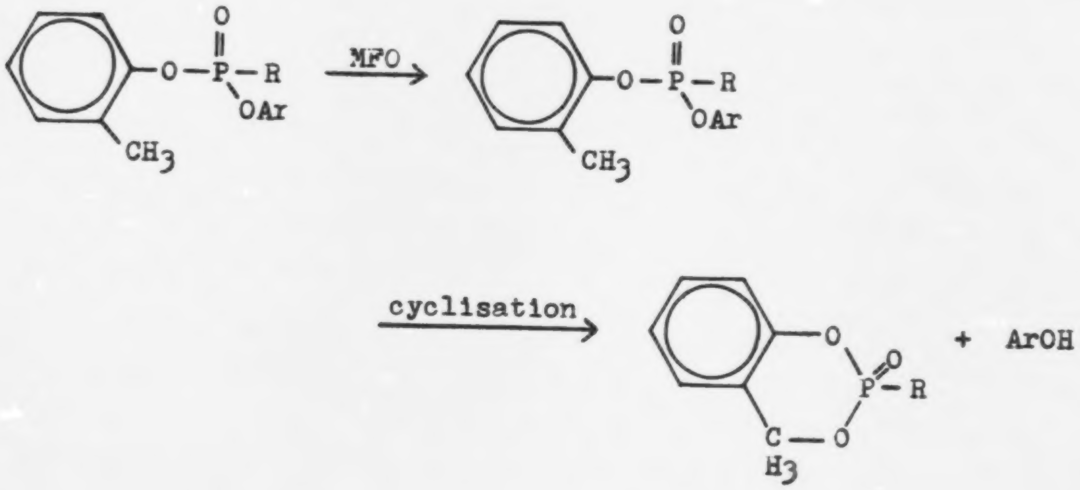


TABLE 5-8 Comparative Neurotoxicities of Tricresyl Phosphate Isomers: Tested in the Chicken[16]

Isomers	Minimum Paralytic Dose (mg/kg)
TCP - mixed	10 to 12
T-o, o, oCP	ca. 240
T-o, o, mCP	30 to 60
T-o, o, pCP	30 to 60
T-o, m, mCP	15 to 30
T-o, p, pCP	15 to 30
T-o, m, pCP	15 to 30

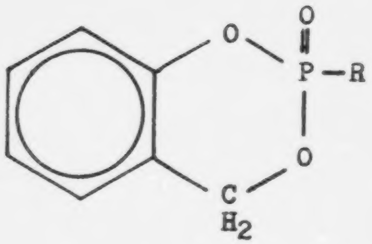
When this cyclic phosphate metabolite of TOCP was tested in chickens, it was found to be a more potent neurotoxin and esterase inhibitor than the native TOCP.[112] An accumulation of the cyclic phosphate metabolite of TOCP, or saligenin cyclic o-cresyl phosphate, has been identified in the liver of TOCP treated chickens, where it was stored for several days after dosing.[109, 110] This compound was also more potent than TOCP in producing degenerative neural changes in chick embryo dorsal root ganglia cell cultures.[110]

While saligenin cyclic o-cresyl phosphate has been well identified as a metabolite of TOCP, the existence of other neurotoxic o-alkylphenyl phosphates indicates similarly neurotoxic metabolites. These phosphates are presumably metabolized into their corresponding saligenin cyclic phosphate through hydroxylation on the α-carbon of the side chain and a subsequent intramolecular rearrangement:[152]



where MFO = mixed function oxidase (hepatic) and R = alkoxy, aryloxy or alkylamido group. Table 5-9 shows the neurotoxicity of several saligenin

TABLE 5-9 The Neurotoxicity of Some Saligenin Cyclic Aryl/alkyl Phosphates in the Hen[153]



R	Minimum Ataxic Dose* (mg/kg)
OPh	1. 5 to 2
OPh-2-Me (the TOCP metabolite)	2 to 5
OPh-3-Me	1 to 3
OPh-4-Me	0. 25 to 0. 5
OPh-3, 5-diMe	4 to 8
OMe	n. a.
Ph	200
Et	n. a.

* n. a. = No ataxia signs evident with any sublethal dosages.

phosphate esters. With respect to this table, it should be noted that only ortho-substituted phosphates can give a cyclic saligenin phosphate.

A few compounds with an ortho-alkylphenyl ester group were not able to produce ataxia in hens (see Table 5-7). This lack of apparent neurotoxicity, although not absolute in all cases, may occur because formation of an active metabolite may proceed too slowly and/or the inhibitory specificity at the neurotoxic site is exceptionally great.[152]

Methyl di-o-cresyl phosphate and di-methyl o-cresyl phosphate are not neurotoxic. Their metabolism yields a cyclic alkyl saligenin phosphate and not a cyclic aryl saligenin phosphate. It is suggested by Eto that only cyclic aryl saligenin phosphates have the ability to cause ataxia.[152]

The significance of Eto's observation is that only triaryl phosphates have a potential to be neurotoxic. Both Johnson and Johannsen demonstrated that short-chain ortho-substituents form compounds that are more neuro-active, as do those with only one substitutent on the benzene ring and fewer subsituted aryl groups in the phosphate molecule.[113, 118] The most toxic compound is, then, o-cresyl diphenyl phosphate.

5.3.3.2 Antiesterase activity: Johnson has put forth the concept of a "neurotoxic esterase" as being the mechanism of action of delayed neurotoxicity.[119] The neurotoxicity has been linked to a specific carboxylic esterase which hydrolyses phenyl phenylacetate. The enzyme is phosphorylated by neurotoxic organic phosphorus compounds, and is inactivated by slow hydrolysis of a phenolic group.

The neurotoxic esterase is assumed to be responsible for the neuron degeneration and observed diagnostic ataxia. The relationship with antiesterase activity appears to be real, as supported by Aldridge[155] who pointed out that all ataxia-producing organophosphorus compounds were esters with a general capacity to inhibit esterases *in vivo*. The relationship is not a simple one, however, and cholinesterase inhibition alone does not explain the neurotoxicity observed, particularly delayed neurotoxicity.

Bloch determined isomer specific responses to TCP: ortho- and meta- isomers inhibited horse serum pseudocholinesterase and ortho- and para- isomers inhibited rabbit pseudocholinesterase.[156,157] A pseudocholinesterase is distinguished from a true or acetylcholinesterase, the former being found in serum, liver and other tissues, and the latter at neuron synapses and in erythrocytes. They differ in their sensitivity to TOCP.[158,159] In humans, rabbits, chickens, and rats, the pseudocholinesterase was inhibited by TOCP about 10 times as strongly as acetylcholinesterase. Such inhibition was also shown to precede the onset of neurotoxicity, and thus the neurotoxic effects of TOCP were initially attributed to the specific inhibition of pseudocholinesterase. Subsequently, however, it was shown that pseudocholinesterase inhibition had little or no bearing on the neural degeneration or paralysis observed. Davidson demonstrated that other organophosphorus compounds, such as diisopropylfluorophosphate (DFP), had a potent anti-pseudocholinesterase activity, but did not cause demyelination or neurotoxicity.[160,161] Mice show no symptoms of TPP intoxication, but do have a marked blood cholinesterase depression.[72]

As discussed previously, it appears to be the metabolites of TAP/AAPs which are active anti-esterases in vivo and presumably bind with cholinesterase and the postulated esterase. Most convincingly for the metabolite hypothesis is that a number of TAPs including TOCP were shown to be active anti-esterases in vivo, while they were not active in vitro where no metabolic formation occurred.[155, 162]

Convincing evidence has been assembled from more recent experimentation which strongly suggests that the anti-cholinesterase, including acetylcholinesterase, activity of TAP/AAPs does not explain delayed neurotoxicity. For instance, two esterases in chicken CNS tissue, using phenyl-2-phenyl acetate and phenyl-3-phenyl proprionate as substrates, were inhibited by organophosphorus compounds causing ataxia in chickens, as well as some which did not.[124] The inhibition of these CNS esterases cannot then be considered relevant to the production of neural lesions. Bondy et al established that there was no consistency among the neurotoxic effects of a number of TAPs and their plasma or brain cholinesterase inhibitory activities.[163] Neurotoxic esterase activity in chicken brain was inhibited similarly at TOCP doses from 11.25 to 500 mg/kg per day for 20 days, but the low doses did not result in neurotoxic signs, such as the leg weakness and paralysis noted at higher doses.[164] A recent and detailed study by Manno et al examines the effect of TCP treatment on a number of esterases (acetylcholinesterase, butyrylcholinesterase, arylesterase, aliesterase, and $NADPH_2$-oxidase) in rat serum, liver and brain.[165] Activities were variously raised or lowered, or not changed depending on tissue type, sex, or the presence of potentiation by hexane. Acetylcholinesterase was inhibited in all cases.

One of the effects of TAP/AAPs has been their marked ability to potentiate insecticides, particularly malathion. As described previously in Section 5. 2. 2. 5 malathion has been shown to be potentiated in its anti-cholinesterase activity in insects, birds, and fish. It appears that the substantiated anti-esterase activity of TAP/AAPs is the correlating factor. When aliesterase, an effective inactivating enzyme for malathion, can be inhibited by the organophosphorus compounds, there will be a concomitant increase in malathion toxicity.[153, 165-167]

The current view appears to be than an inhibition of acetylcholinesterase and consequent cholinergic action by TAP/AAPs may explain the acute toxic effects of these compounds. The delayed neurotoxic effect may involve the anti-esterase activity of a more potent neurotoxic metabolite, such as 2-(o-cresyl)4H-1, 3, 2-benzodioxaphosphoran-2-one, which actually binds to esterases. Again there are other recent explanations for the delayed neurotoxicity effect which do not involve an active metabolite. For instance, TOCP as a parent compound has been shown to greatly inhibit Na^+, K^+-stimulated and Mg^{2+}-dependent ATPases in neuronal membranes. An obvious effect on neuronal membrane metabolism is a consequence of ATPase inhibition, which may be postulated to explain the delayed neurotoxicity in vivo.[168] Another new concept, postulated by Bischoff,[169] may be useful to explain, for instance, the inability of Morazain and Rosenberg[170] to detect anti-cholinesterase metabolites in the spinal cord or sciatic nerve of TOCP-poisoned chickens. Hypothetically, normal structural phosphates in the axonal membrane might be replaced by TOCP molecules with a consequent steric reorientation of phospholipids in the membranes. This would have a direct effect on axon function. The hypothesis is supported by autoradiographic evidence showing incorporation of TAP into structural lipid elements of the nervous system.[169]

The entire question of the mechanism of delayed neurotoxicity still seeks definition. It may be that the neurotoxic effect may have to be attributed to several causes.

5.3.4 Additional Toxicity Effects

A number of enzymes other than strict esterases have been shown to be affected by TAP exposure. The activity of tributyrinase of the spinal cords of chickens was found to be moderately reduced, although other enzymes assayed, such as those of glucose and pyruvate oxidases, trypsin, brain amine oxidase, pancreatic lecithinase and brain cephalinase were found to be not affected by TOCP.[171] Neural membrane ATPases were inhibited.[168] Another recorded enzymatic TOCP effect was an inhibition of the hydrolysis activity of triacetin.[172] An induction of liver enzymes associated with the metabolism of TCP was noted, particularly increased activity of microsomal NADPH-oxidase as well as that of a microsomal hepatic arylesterase.[165] None of these enzyme activity variations could be associated with any clinical response and thus are probably secondary to the overt toxicity effects.

A number of tissues and organs other than nervous tissues have been affected by TOCP and other TAP poisoning experiments. Myopathy has been cited by Zil'ber _et al_ as a consequence of TCP and TXP poisoning in guinea pigs.[173] Electron microscopic observations of foot muscles in TOCP treated (0.75 to 1.0 mL/kg) cats showed pathologic inclusions and alterations in the normal contractile ultrastructure, resembling a "spheromembranous degeneration".[174]

In rabbits, dogs, cats and guinea pigs, high doses of TOCP have been identified with capillary changes evidenced by hyperemia and hemorrhages in gut, liver, spleen, pancreas and other organs. An extensive epithelial desquamation and leucocytic infiltration was noted in gut tissue. An interstitial pancreatitis and necrosis of adipose tissue resulted in treated dogs.[107]

Gonadal tissue and function may also be affected, perhaps by way of a steroid imbalance. Doses of 100 to 500 mg/kg TCP for 20 days in dogs resulted in testicular degeneration.[131] Guinea pigs as well showed testicular degeneration at doses of TCP and TXP as high as 2.1 g/kg/day.[173] In a study on female rats, TCP was shown to prolong the oestrus period and shorten rest phases. The ovaries were affected at doses of TCP which caused no overt toxicity symptoms.[175]

Some evidence of skin irritation or sensitization has been presented. The presence of TCP or TPP in the cellulose acetate film of patch tests in carbon paper, or other plastic objects has resulted in contact dermatitis reactions in a small number of human patients who had become sensitized to the TAPs.[176,177] Another patch test on the skin sensitization to Santicizer 141 (2-ethylhexyl diphenyl phosphate) showed no reactions or contact dermatitis.[178]

Studies were conducted on the involvement of autoimmunity in the pathogenesis of TOCP-induced neurotoxicity in chickens.[179,180]

Neurotoxic doses of TDCP increased diffuse lymphatic tissue and plasma gamma-globulin, suggesting a stimulation of the immunologic response in chickens. Immunosuppressive therapy, however, gave no protection against the neurotoxic effect. Tests of auto-immunity failed to show such a response to nervous tissues or liver in TOCP intoxicated chickens.

Limited evidence exists at this time for carcinogenic or mutagenic effects of TAP/AAPs. Tests carried out by the Stauffer Chemical Company and made available to the authors of this report[127] have shown that of the two compounds listed in Table 5-10, only IPDP can be said to show some evidence of mutagenicity. There was a transformation of mouse BALB/3T3 cells in culture on exposure to IPDP, as well as some indication of a positive forward mutation in activated L5178Y TK+/-mouse lymphoma cells. This is, to date, the only reported mutagenic effect of TAPs. Carcinogenesis has not been suggested.

A test for teratogenicity of TOCP, among other compounds, was found to be negative. High doses of TOCP in chick embryos had little effect in decreasing embryo levels of nicotinamide adenine dinucleotide (NAD). (A decrease in NAD was noted with other toxicants and did result in teratogenic effects.) No effects were noted in chicks hatched from TOCP-treated embryos.

5. 3. 5 Nutritional Relationships

It has been stated repeatedly that the degenerative changes of the motor nervous system accompanying delayed neurotoxicity caused

TABLE 5-10 Summary of in vitro Mutagenesis and Carcinogenesis Testing by Stauffer Chemical Company of Triaryl Phosphates[127]

Compound	Test	Result
IPDP	Ames *Salmonella* microsome plate assay	negative in activated and non-activated preparations
	Transformation of mouse BALB/3T3 cells in culture	positive
	Mouse lymphoma L5178YTK+/- cell line forward mutation assay	negative without activation; weakly positive with activation
	Sister chromatid exchange in L5178Y mouse lymphoma cells	negative in non-activated and in activated preparations
	Chromosome aberration in L5178Y mouse lymphoma cells	negative in non-activated and in activated preparations
BPDP	Ames *Salmonella* microsome plate assay	negative
	Transformation of mouse BALB/3T3 cells in culture	negative
	Mouse lymphoma L5178YTK+/- cell line forward mutation assay	negative
	Sister chromatid exchange in L5178Y mouse lymphoma cells	negative
	Chromosome aberrations in L5178Y mouse lymphoma cells	negative

by TAP/AAPs closely resemble those of a thiamine (vitamin B_1) and nicotinic acid deficiency.[134, 135] The suggestion is made that there is a biochemical lesion involving the permanent blocking of a vital synthetic pathway, or that at least there is a mechanism producing neuronal damage common to both conditions. The administration of thiamine or nicotinic acid does not, however, prevent or alleviate the delayed neurotoxicity due to TAP/AAP poisoning.

There appears to be an interference with fat-soluble vitamins by TOCP in rats.[182] Additional dietary vitamin E (tocopherol) partially prevented the growth inhibition of rats fed TOCP and normalized tissue lipids, particularly arachidonic acid levels. Vitamin E levels decreased, as did liver vitamin A deposition, with TOCP treatment. The relationship may be a simple one in that TOCP is a pro-oxidant and both vitamins E and A are readily oxidized. It is of interest here to note that the addition of casein to the diet normalized growth, vitamin E levels, and tissue lipids even in the presence of TOCP treatment. The decrease of arachidonic acid caused by TOCP was greatly accentuated in an essential fatty-acid-free diet.[183] TOCP treatment generally increased the severity of an essential fatty-acid-free diet in rats.

The relationships between nutritional adequacy in fat-soluble vitamins and in essential fatty acids and TAP/AAP toxicity effects definitely requires further examination. Similarly, nutritional adequacies in thiamine and nicotinic acid should be examined further in relation to the expression of neurotoxicity.

5.4 SUMMARY

The majority of toxicological studies carried out on environmentally significant species have been on fish. Absorption of TAP/AAPs occurs primarily through gill surfaces, although oral dosing has also caused toxicity effects. Bioaccumulation, by factors of several hundred or more depending on the specific TAP/AAP, has been shown to occur. Gastrointestinal absorption has been demonstrated experimentally in cattle.

In aquatic organisms, particularly fish, LC_{50} values have been determined for a large number of TAP/AAPs with a wide variation in values obtained, both with respect to different species and the individual TAP/AAPs. Neurotoxicity has also been demonstrated in mammals, including cattle and other species of domestic or economic importance, receiving acute doses. Histopathology correlates with the neurotoxic signs, marked by progressive motor paralysis. Axonal degeneration preceded a myelin degeneration, commencing usually in peripheral systemic tracts and progressing centrally in more severe cases. The onset of neurotoxic signs may be delayed, or remit, and then show a progressive involvement. Recovery is slow. Death may result in cases of exposure to large doses. There can be no overall generalization regarding the effects of TAP/AAPs -- these depend on the nature of the specific compound or commercial mixture, species affected, and also, probably, on the sex of the animal.

Studies of chronic effects also show a progression of neurotoxicity in fish and other biota, demonstrated particularly by behavioural abnormalities. Limited changes in hematological parameters and plasma chemistry accompany TAP/AAP contamination in fish. Rainbow trout appear to be the most sensitive piscine species.

Many experimental studies have shown that TAP/AAPs can potentiate the action of organophosphorus insecticides (e. g. , malathion) in both target and non-target species. This synergism is linked to the toxicity mechanism of TAP/AAPs in that they inhibit esterases (such as acetylcholinesterase). Triaryl/alkyl phosphates may inhibit ali-esterases sensitive to malathion, for example, potentiating the effect of a dose of the latter in the inhibition of neural cholinesterase.

Experimental studies using laboratory animals and procedures form the bases for the description and explanation of TAP/AAP toxicity. Absorption by way of skin or gut is rapid in mammals, as is the loss rate by way of excretory routes (urine, feces, bile). Storage of absorbed TAP/AAPs occurs in a variety of body tissues and is most prominent in the liver, a particular site of TAP/AAP metabolism.

Acute toxicity effects observed in studies on laboratory animals relate particularly to the anti-esterase activity of high doses of TAP/AAPs, which lead to paralysis, dyspnea and death. Delayed neurotoxicity appears one to two weeks after the poisoning event, without the appearance of symptoms during the intervening time. The effects commence with a flaccid paralysis and ataxia in the rear limbs, progressing to forelimbs and perhaps, in severe cases, involving trunk musculature. The degree of involvement is dependent on both dose and the TAP/AAP compound. Of the many laboratory test species used, the chicken and cat appear to be the most sensitive. Neuropathology shows the primary lesion to be axonal, leading to a demyelination and a decrease in conductive velocity of nerve impulses. The type of neurotoxicity, particularly for TOCP, has been commonly described as a Wallerian degeneration.

Structure-activity relationships have been established which show that only triaryl phosphates are likely to be neurotoxic, and then only if the TAP contains an ortho-substituted aryl group containing an alkyl group with at least one α-hydrogen. The neurotoxic metabolite has been shown to be a saligenin cyclic aryl phosphate. The connection between delayed neurotoxicity and anti-esterase activity of TAP/AAPs is uncertain and is used mainly to explain acute neural effects. Anti-esterase activity by the saligenin cyclic metabolite may relate to delayed neurotoxicity.

Other toxicity effects have also been demonstrated. This includes inhibition of ion-dependent ATPases in neuronal membranes, which may be a link to neurotoxicity. A number of clinical and metabolic enzymes have inconclusively been shown to be affected in various tissues Some effects on reproductive function have been demonstrated. No carcinogenesis or mutagenesis has been demonstrated and teratogenesis has not been found. Correlations between dietary adequacy for the vitamins thiamine, nicotinic acid and tocopherol and the severity of TAP/AAP intoxication have been suggested.

6. HUMAN HEALTH EFFECTS

6.1 INTRODUCTION

Although the literature on the human health effects of TAP/AAPs is quite extensive, much of the information discussed is based on a small number of critical TAP intoxication events. These are for the most part accidental or episodic in nature and in that sense, environmental in association. Typically, and as should be expected, very little experimentation and information exist from experimental or volunteer studies. These were discussed as appropriate in the previous chapter (Section 5.3.1).

As in the experimental studies, it is TOCP in particular which has been associated with the most severe toxicity effects. Other TAP/AAP compounds have shown similar effects at much higher concentrations, at least to the degree to which they have been examined.

6.2 HUMAN EXPOSURE INCIDENCES

6.2.1 Incidental or Accidental Exposures

The majority of exposure incidences have been of an incidental and episodic type, marked by the sudden onset of a small or large number of cases in a defined geographic region. These TAP intoxication incidents have also been the most spectacular in effect and setting. These episodic poisonings have been associated with ingestion of TOCP containing substances, frequently in food preparations. The tasteless and odourless character of TAP oils faciliated such error.

The earliest recorded poisoning was reported by Loret.[184] Six cases occurred among patients given a TOCP-containing phosphocreosote cough mixture.

The majority of cases and reports have dealt with the so-called "ginger jake" paralysis syndrome. The 1930 prohibition in the United States prompted a large number of people to use, as an alcohol substitute, a "Fluid Extract of Ginger (USP)" containing about 75% ethanol.[185] This product contained 2% TOCP, the source of which has never been identified. An estimated 10,000 to 15,000 people, however, throughout the United States have been identified as affected. Typically these tended to be hard drinkers. A large descriptive literature of effects has been established on this episode.[114, 134, 186-193, 219]

Several hundred women were poisoned in Europe in 1931 by an apiol pill, an extract of parsley, taken as an abortifacient.[194] Tricresyl phosphate had apparently been added to the preparation as an additional abortion stimulus.

An episode in Durban, South Africa, resulted in the affliction of 68 people by TOCP.[195, 196] It arose from cooking oil that had been stored in drums contaminated by previous use for a TOCP containing oil.

Another cooking oil episode occurred in 1940 in the Swiss army. There, food was erroneously prepared in machine gun cooling oil which had been stored in olive oil cans. Eighty men were affected, in degrees varying from mild to severe intoxication.[197,198]

A number of factory workers in Germany during the second world war were poisoned by TCP which they had taken home as a fat substitute for cooking.[199] A further small incident of intoxication resulting from TOCP occurred in 1945 in Liverpool. Seventeen people were affected by using TOCP-contaminated cottonseed oil for cooking.[200]

Another outbreak in Durban in 1955, which involved 11 patients, was suggestive of TOCP contamination of drinking water, stored in drums having held TOCP-containing paint.[201]

A major outbreak of poisoning occurred in Morocco in 1959. Obsolete turbo-jet engine oil, containing TCP compounds was used to dilute olive oil, giving a product containing about 3% TCP. Over 10,000 cases were traced to this contamination and described in detail.[202-205]

Incidental and unwitting contamination of people by TOCP in solid foods has also occurred, once in 1962 in India[206] and in 1967 of 56 people in Fiji.[207] Each episode was traced to a single batch of TOCP contaminated flour.

6.2.2 Occupational Exposure

One instance of primary and probably acute exposure concerns three cases in England in 1942.[117] The men worked in poorly ventilated black-out conditions in a factory producing TCP and TPP. The workers were probably poisoned and paralyzed by TCP vapours resulting from hot TCP washing procedures. Hunter et al specifically implicated TOCP as the active agent.[117] Presumably the route of entry in this instance was through the lung, and perhaps the skin epithelium.

Other studies of occupational exposure have been assessments of chronic work-related exposures.

Tabershaw and Kleinfeld identified minor signs and symptoms in workers in a factory manufacturing TPP and TCP.[71] A depressed pseudocholinesterase value was the most prevalent sign. The degree of TAP related effects was of minor overall effect to the workers' health. No significant TAP related effects were found in aircraft carrier personnel assigned to the clean-up of aircraft elevator hydraulic fluid spills.[208] This fluid contained TAP oils. Although vapour inhalation and skin contact had occasionally occurred, generally effective clean-up of personal contamination prevented TAP toxicity effects.

A number of other studies assess worker exposure hazard in the manufacture of TAP compounds. Sutton et al detail the lack of adverse clinical effects in workers of a plant manufacturing TPP.[72] Some workers were exposed for as long as ten years. A number of Russian researchers have recently been assessing the hazard of TAP production to workers. Nekhamkina et al[217] describe blood chemistry changes with chronic TAP intoxication, preceding any paralytic signs. Pashkova reported that one third of workers engaged in the manufacture of TCP showed menstrual cycle irregularities related to endocrine disturbances.[175] Some suggestion of gonadal effects has also been made for factory workers by Kalinina.[209] Most recently, Aizenshtadt identified a progression of toxicity effects in a study of 253 TAP-manufacture associated workers.[210] A neural involvement was indicated, including the autonomic nervous system. It should be noted that the workers were exposed not only to TAP compounds (TCP, TPP and TXP), but also to cresols, phenols, and phosphorus oxychloride. This less specific exposure may explain some of the more unusual (as far as TAP toxicity is concerned) symptoms noted by Aizenshtadt.

It is of comparative interest here to cite the findings of Cosi _et al_ in female shoe-workers suffering from polyneuritis and paresis of the lower extremities.[211] Detailed examination of the symptoms points to TCP intoxication, but neither TCP nor any other substance was found in the glues and adhesives used in shoe manufacture. Assuming that there was no unaccounted incident of exposure to TAP, this study serves to emphasize that the overt and clinical signs of TAP intoxication are not restricted to these contaminants, but are associated with a wide **spectrum** of neurologic diseases, including ones induced by chemicals other than TAP/AAP compounds.

6.3 TOXICITY EFFECTS

6.3.1 Symptoms

The bulk of information on overt toxicity effects in humans is derived from major episodic non-occupational contaminations. These implicate TOCP in particular as the active agent.

As summarized from the references cited in section 6. 2. 1, overt symptoms occurred soon after the ingestion intoxication event and persisted usually for several days. The first symptoms were gastrointestinal of varying degree, ranging from slight to severe nausea and vomiting, possibly including epigastric pain and abdominal cramps, and in some cases diarrhea. In some cases, diarrhea lasted for several weeks. These initial symptoms may or may not have been present, depending on the individual susceptibility, the strength of the TAP dose, and the route of exposure. These early clinical manifestations of intoxication disappeared within one week to a month, if they were present at all. In the case of chronic low level exposures, these symptoms may not have been present and the only symptoms may have been the onset of a delayed neurotoxicity after even several months of chronic intoxication.

The delayed symptoms are neurological disturbances, evidenced initially by tingling sensations and numbness in the feet, perhaps associated with soreness and cramps. This paresis may take as little as one week to develop after the intoxication event or onset. The lower peripheral neurologic disturbance increases in severity and in perhaps 48 hours after onset gives rise, even suddenly, to a paralysis of the toes. The paralysis is flaccid and typically proceeds proximally to extend to thigh and hip musculature. It may involve the hands and arms if the exposure was particularly high. The effects are bilaterally symmetrical. The paralysis is almost entirely motor; sensory impairment is not a diagnostic feature, although stereognostic and joint senses and motor reflexes might be impaired. Sphincter musculature and autonomic nervous system impairment has not usually been associated with TAP (TOCP) poisoning. In some particularly severely affected patients, the muscular weakness and loss of power extended to abdominal and lumbar muscles, as well some loss of peripheral sensation and sphincter control.[193] Some wasting of muscles in the extremities, particularly distally, has been reported.

Subjectively, the patients would complain of pain, particularly in the feet and legs, cold hands and feet, and a loss of power leading to inability to walk and even feed themselves.

Another symptom of TAP/AAP poisoning is the induction of a contact dermatitis. A number of consumer products, specifically their TAP components, have been linked with occurrence of allergic dermatitis. These have included eyeglass frames,[212] carbon paper, cellulose-lacquer, plastics,[176] and a number of polyvinyl chloride household products.[177] The incidence of TAP/AAP allergic sensitivity is very low, only 0.02% in a sample of 23,000 allergy patients, and thus has to be considered a rare condition and not a hazard to the population in general.[176] Dermatitis has been reported in industrial settings. Workers involved in TCP and TPP manufacture showed a greater incidence of skin disorders.[213]

6.3.2 Prognosis

From the onset of muscular weakness, the disease usually progressed until about one to two months after onset. The degree of progression appeared to be dose related. The incidence of fatality attributable to TAP/AAP poisoning is very low and few deaths from respiratory paralysis have occurred.

Recovery from the poisoning is very slow and may take months or years, again related directly to the total dose received and the severity of consequent neurological symptoms. The sequence of recovery generally proceeds in reverse order to the involvement; arms and hands, for instance, show an earlier recovery than the lower extremities.[214] Recovery commences with a very slow improvement in strength and a remission of the pain. Severe cases may never recover completely, most likely because of damage to spinal cord neural tracts.[202] In the Swiss army outbreak, for instance, where TOCP poisoning was severe, 25% of the patients were reported as permanently disabled,[198] In cases of delayed or non-recovery, the flaccid paralysis changes to a spastic paralysis in approximately one year.[192, 198, 214, 215]

6. 3. 3 Pathology

Histopathological examination of neural tissues of patients afflicted by Jamaica ginger ("jake") paralysis indicated a degeneration of myelin sheaths of the peripheral nerves, with a variable amount of central degenerative changes affecting the anterior horn cells throughout the spinal cord, but more often the lumbar and cervical regions. The columns of Groll and lower pyramidal tracts in the spinal cord may be affected. In the acute phase, there is chromatolysis of the cells of the anterior horns of the spinal cord, while in the chronic phase these cells are reduced in number. Essentially similar lesions were produced experimentally by TOCP in laboratory animals, including dogs, monkeys, cats and chickens.[114, 120, 155, 158, 193, 216] It is of interest here to elaborate that Aring had attributed the nerve and muscle pathology resulting from "jake" poisoning to a primary hyperplastic fibrosis of the smaller arteries and capillaries, which appears to begin to develop in the latent period between ingestion of the poison and appearance of neurological signs.[193] This view has not been generally accepted nor substantiated by animal experimentation.

Muscle pathology is associated with the progressively later symptoms of muscle wasting. In the TOCP-poisoning case in the Swiss army, muscle lesions were recorded, and persisted three and one-half years after the neuritis was healed.[198] Muscle biopsies from patients poisoned by TAP in the Morocco episode, examined after one and a half years, showed reduced numbers of motor axons, abnormal innervation patterns, muscle atrophy, and evidence of axon regeneration. There were no changes in the sensory apparatus.[215]

Little information is reported on clinical chemistry or on hematological changes resulting from TAP/AAP intoxication incidences marked by overt symptoms. Examination of cerebrospinal fluid showed no significant alterations, with perhaps a slight rise in protein levels. All hematological parameters were normal.[200, 202] Cholinesterase changes are presumed to parallel those in animal experimentation, but were not actually tested in the various acute poisoning episodes.

Identification of early signs of intoxication at the level of plasma chemical or hematological level would be of great benefit, particularly if these changes occurred prior to the onset of more severe neurological symptoms. Health monitoring in occupational settings has revealed that TAP/AAP induced changes occur in workers. In a factory manufacturing TAP, about one half of the workers examined showed significant decreases in pseudocholinesterase, and many of them had minor signs and symptoms.[71] In cases of occasional inhalation and skin exposure to TAP-containing hydraulic oil, however, aircraft-carrier sailors who were exposed showed no changes in cholinesterase activity.[208] In the case of a group of men regularly engaged in TPP manufacture, there was a significant reduction in erythrocyte cholinesterase activity. Even though these men had been exposed for up to 10 years to TPP vapour, mist and dust, at a time weighted average concentration of 3.5 mg/m^3, they showed no evidence of adverse clinical effects.[72] This supports the evidence gathered in animal experimentation that a decrease in blood cholinesterase activity is not a monitor of toxicity *per se*, but can be used as an assessment of total exposure to TAP/AAP compounds. Other evidence has been gathered for workers employed in TAP production in the USSR. Chronic intoxication with TAP plasticizers was associated with decreased plasma and erythrocyte cholinesterase activity, as well as an increase in oxidized glutathione and plasma protein sulphydryl groups, all of which preceded clinical manifestations and are suggested as an early diagnosis of phosphate plasticizer poisoning.[216] Aizenshtadt reports a number of clinical manifestations in workers, engaged in the manufacture of TAP compounds, exposed to TCP, TXP, TPP and other compounds.[210] A dominant symptom, among others, was a reduced foot extension force. The clinical signs were accompanied by a decrease in plasma cholinesterase activity. It has been suggested that blood ion determinations may be used to supplement an early diagnosis of intoxication.[218] Exposure to triaryl phosphate plasticizers for up to 14 years decreased serum levels of K^+ and serum and erythrocyte Ca^{2+} levels and increased serum and erythrocyte Mg^{2+} concentrations.

6.4 SUMMARY

An acute intoxication episode by ingestion is commonly associated with nausea, vomiting, abdominal cramps, and diarrhea as early signs. At a given dose, the severity of the immediate effects appears to show a great individual variability. Further, the degree of acute effects bears little relation to the degree of delayed symptoms, marked by the development of paralysis. The delayed paralysis effect may occur one week to a month after an acute exposure, or take much longer to develop in instances of prolonged low level exposure. There is some suggestion that the neurological effects are additively dose-dependent; that is, long-term low dose exposures appear to show an almost direct relationship to the cumulative dose level.

The delayed neurological effects involve long axon sensory and motor nerves. The effects are progressive and generally commence in lower extremities. Muscular cramps, soreness, numbness, and tingling sensations in the feet, calves, and thighs are followed by flaccid paralysis in the toes. The paralysis, if unchecked by removal from exposure in cases of chronic contamination, gradually extends proximally to involve the legs. In instances of high dose exposure or presumably high individual sensitivity, the neuropathology may extend to the upper spinal cord and show consequent paralysis of the hands and arms. The upper central nervous system and the autonomic nervous system are little affected. Clinical diagnosis of TAP/AAP intoxication, acute or chronic, has been limited to depressed cholinesterase activity, particularly of blood pseudocholinesterase.

Thus, in summary, the human picture of TAP/AAP poisoning closely approximates the animal models, including the delayed appearance of neurological signs, long recovery times, and the lack of positive correlation between overt effects and blood cholinesterase changes. Nonetheless, the measure of cholinesterase activity can be used as an early diagnostic measure, including chronic exposure. Although almost all the information on human toxicity effects specifies or implicates TOCP as the toxicologically active compound, it is reasonable to assume, on the basis of animal experiments, that other TAP/AAP compounds may have effects in humans similar to those shown in pharmacological studies. The differences are likely those of degree as related to intensity of poisoning dose, similar to what has been found in the animal experimentation.

7. REGULATIONS AND GUIDELINES

7.1 INTRODUCTION

Obtaining information on regulations and guidelines concerning potentially hazardous chemicals is complicated by the fact that regulatory topics are not normally covered by standard reference sources such as Chemical Abstracts. In an attempt to secure the appropriate information, approaches were made to Canadian embassies (in France, Japan, Sweden, the United Kingdom and West Germany) and to the World Health Organization's International Register of Potentially Toxic Chemicals (IRPTC) in Geneva asking for information concerning regulatory approaches to TAP/AAPs adopted by a number of countries. Information received was, however, fragmentary, perhaps indicating that few regulatory measures have been taken.

The International Labour Office lists 12 countries that have occupational exposure limits for TOCP and TPP.[220] The ILO publication dealt with the situation extant in 1976 and it is not known whether the limits have changed since then.

Current information pertaining to eight countries; Canada, France, Japan, Sweden, Union of Soviet Socialist Republics, United Kingdom, United States and West Germany, was obtained. Information was sparse and varied from country to country, making intercomparison impossible.

7.2 THE ACGIH RECOMMENDATIONS

The American Conference of Governmental Industrial Hygienists (ACGIH) recommends exposure limits (called Threshold Limit Values - TLV ®) which refer to airborne concentrations at which it is believed that the great majority of workers may be repeatedly exposed, on a daily basis, without adverse effects. While the ACGIH does not list a TLV for TAP/AAPs as a group, two individual compounds, tri-o-cresyl phosphate and triphenyl phosphate, have been assigned TLVs.[221]

For TOCP the TLV is 0.1 mg/m^3, expressed as a time weighted average for an eight-hour workday. In addition, a short term exposure limit (STEL) of 0.3 mg/m^3 is recommended. A STEL represents the maximum concentration to which a worker may be exposed in a single event lasting not longer than 15 minutes. The corresponding exposure limits for TPP are a TLV of 3 mg/m^3 with a STEL of 6 mg/m^3.

It should be noted that many countries and most Canadian provinces adopt ACGIH Threshold Limit Values as permissible exposure guidelines. The Occupational Safety and Health Administration has adopted ACGIH threshold limit values as an interim measure in situations where OSHA has not yet set its own standard.

7.3 INDIVIDUAL COUNTRIES

Neither Canada (with the exception of provinces which adopt ACGIH occupational exposure levels) nor Japan[222] has any form of regulation aimed at controlling TAP/AAPs. The other countries discussed in this section have regulations or guidelines which range from the very general to the specific.

7.3.1 France[223]

Nothing very specific appears to exist regarding TAP/AAPs. There is a general principle regarding control or banning of phosphate esters (unspecified) for environmental protection purposes. This guideline states that "Les rejets sont traités cas par cas, selon la procédure habituelle décentralisée". There is a specific requirement that tri-o-cresyl phosphate be labelled as a toxic substance.

7.3.2 Sweden[224]

Tri-o-cresyl phosphate has been classified as a poison. This designation implies that TOCP must not be present in significant quantities in any consumer product. In addition, regulations require that TOCP only be used after notification to and special permission from the occupational safety and health authorities.

7.3.3 Union of Soviet Socialist Republics[224]

The USSR has regulations dealing both with the use of TAP/AAPs in workplaces and with aryl phosphates in drinking water.

7.3.3.1 Occupational health: The maximum allowable concentration (MAC) in workplace atmosphere for TCP containing more than 3% ortho-isomers is 0.1 mg/m^3, while the MAC for TCP containing less than 3% ortho-isomers is 0.5 mg/m^3. Maximum allowable concentrations for TXP and tris (2-ethylhexyl) phosphate are 1.5 mg/m^3 and 0.1 mg/m^3, respectively. In addition, these three phosphate esters have been identified as noxious by skin absorption and the use of protective clothing is required.

7.3.3.2 Drinking water: Maximum allowable concentrations in drinking water for TCP and TXP have been established. That for TCP, which refers to mixtures containing more than 3% ortho-isomers, is set at 0.005 mg/L while the limit for TXP is 0.05 mg/L.

7.3.4 United Kingdom

No regulations aimed at health protection from exposure to TAP/AAPs were found. But under the National Insurance (Industrial Injuries) Act, 1965, poisoning by TCP and poisoning by TPP are prescribed diseases.[225] A worker diagnosed to be suffering from a prescribed disease may claim benefit under the Act.

7.3.5 United States

The United States has regulations concerning the use of TPP and EHDP in food packaging. Both these compounds are allowed as additives used in food packaging materials.[226] In addition, EHDP is an acceptable plasticizer for food-contact surfaces[227] (e.g., plastic containers for food and beverages). The regulation stipulates that the plasticizer extracted by a container volume of chloroform should not produce a solution containing more than 50 ppm of the plasticizer.

Permissible levels in the workplace atmosphere are set for TOCP and TPP at the ACGIH TLVs of 0.1 mg/m^3 and 3 mg/m^3 respectively.[220]

7.3.6 West Germany

West German protection and safety guidelines identify a number of precautionary measures that should be taken with TCP:[228]

close containers tightly,
keep away from foods,
avoid skin contact,
avoid eye contact,
wash hands after contact,
avoid contamination of clothing.

These guidelines are aimed at the workplace and appear designed for labels and warning notices.

There are recommended disposal methods for both TCP and TPP.[224] These methods require the aryl phosphate be mixed with sand and limestone and incinerated. It is recommended that such an incinerator be equipped with an after-burner and an alkaline scrubbing system.

7.3.7 Occupational Exposure Limits

The occupational exposure limits for TOCP and TPP in 12 countries are listed in Table 7-1. With the exception of one country, Romania, the limits correspond to the values of the ACGIH Threshold

TABLE 7-1 Permissible Occupational Exposure Limits (mg/m^3) for TOCP and TPP in a Number of Countries*

Country	TOCP	TPP
Australia	0.1	3
Belgium	0.1	2
East Germany	0.1	-
Finland	0.1	3
Italy	0.1 (H)	-
Netherlands	0.1	3
Poland	0.1 (H)	-
Romania	2 av. (H) 5 max.	2 av. 4 max.
Switzerland	0.1	3
USA	0.1	3
USSR	0.1 (H)	-
Yugoslavia	0.1	3

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* Information published by the International Labour Office[220] and, with the exception of the current values for the USA and USSR, the limits represent the situation extant in 1976.

(H) Identified as a skin irritant.

Limit Values. In addition four countries (Italy, Poland, Romania and the USSR) identify TOCP as a skin irritant.

Eight countries (Australia, Belgium, East Germany, Italy, Netherlands, United States and Yugoslavia) have limits which are time weighted averages for a working day, three countries (Poland, Switzerland and the USSR) have limits that can be regarded as ceiling values, while Romania has both time weighted average and ceiling value limits. In seven countries (East Germany, Poland, Romania, Switzerland, United States, USSR and Yugoslavia) the limits have legal force while in the other five the limits serve as recommended guidelines.

7.4 SUMMARY

The regulatory approaches outlined above are illustrations of a whole range of options (workplace exposure limits, compensatable industrial diseases, labelling requirements, disposal guidelines, allowable additives and so on). But no country was determined to have a comprehensive set of regulations dealing with TAP/AAPs. This does not, however, mean that comprehensive regulatory approaches are non-existent -- merely that we were unable to discover any. The conclusion of the Midwest Research Institute, reached after contact with 80 individuals and agencies in both the United States and other countries, is probably representative of the situation -- "phosphate esters are not heavily regulated, nor considered a health, safety or environmental hazard when properly utilized".[8]

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ABBREVIATIONS USED FOR PHOSPHATE ESTERS

triphenyl phosphate	TPP
tricresyl phosphates	TCP
(tri-o-cresyl phosphate)	TOCP
trixylyl phosphates	TXP
cresyl diphenyl phosphate	CDP
isopropylphenyl diphenyl phosphate (mixed isopropylphenyl/phenyl phosphates)	IPDP
t-butylphenyl diphenyl phosphate (mixed butylphenyl/phenyl phosphates)	BPDP
tri-isopropylphenyl phosphate	TIPP
nonylphenyl diphenyl phosphate	NPDP
cumylphenyl diphenyl phosphate	CPDP
dibutyl phenyl phosphate	DBPP
2-ethylhexyl diphenyl phosphate	EHDP
isodecyl diphenyl phosphate	IDDP
tris-2-ethylhexyl phosphate	TEHP